Revue Roumaine de Chimie, **2008**, *53*(4), 273–276

SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL 2-HYDROXY-*N*-(2-TRIFLUOROMETHYL-PHENYL)-BENZAMIDE DERIVATIVES

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Received November 11, 2007

In order to obtain biological active compounds, the synthesis of some new derivatives with *o*-hidroxibenzamidic structure was achieved. Starting from 2-hydroxy-*N*-(2-trifluoromethyl-phenyl)-benzamide and ethyl α-halogenated acid esters were obtained ethyl esters, which were condensated with hydrazine giving hydrazides. In reaction between hydrazides and chloro-substituted benzaldehydes were obtained hydrazones. All new synthesized compounds were characterized by physico-chemical methods (FTIR, ^{1}H-NMR, ^{13}C-NMR, MS), which confirmed their structures.

INTRODUCTION

The research for new biological active compounds represents one of the most important directions of current medicinal chemistry. Salicylanilides, as well as *O*-substituted salicylanilides, are a class of compounds with a broad spectrum of biological activity,[1,2] including the antimicrobial effect against a number of yeast and filamentous fungi. Substitution of phenoxiacetic acid with an electrophile group in *orto* or *para* position increases their activity against human pathogenic fungi.[3-9]

Salicylamide-*O*-acetic hydrazide and its hydrazones obtained with substituted benzaldehydes show anti-inflammatory and analgesic activity superior to salicylamide itself and lower ulcerogenic activity.[10,11]

In order to obtain such active compounds, some *ortho*-substituted phenoxyalkanoic acids and their derivatives were synthesized and characterized.[12,13]

The goal of this research was to synthesize new 2-hydroxibenzamide derivatives with potential antibacterial and antifungical activity and to get a complete characterization of them, using modern physico-chemical methods.

RESULTS AND DISCUSSION

The synthesized compounds, presented in Table 1, are white crystalline substances (needless or prisms) and were obtained with yields ranged between 68-94%.

The obtaining pathways of the synthesized compounds are presented in Scheme 1. The experimental results suggested that the 2-hydroxy-*N*-(2-trifluoromethyl-phenyl)-benzamide derivatives were readily separated and gave pure compounds.

IR spectral data of ethyl esters indicate the presence of ether bond between phenolic hydroxyl and alkyl α-C atom of ester by signals at 1224, 1233 cm^{-1} (ν^{as}COC aromatic) and 1095, 1062 cm^{-1} (ν^{as}COC alifatic). Carbonyl group from esters (νC=O) appears at 1720 and 1757 cm^{-1}, but, in IR spectra of the hydrazide, this band is missing, proving the conversion of the ester into hydrazide. The signals corresponding to the vibrations of the amidic and hydrazidic group appear between 3220-3340 cm^{-1} (νNH) and 1550-1720 (νC=O) cm^{-1}.

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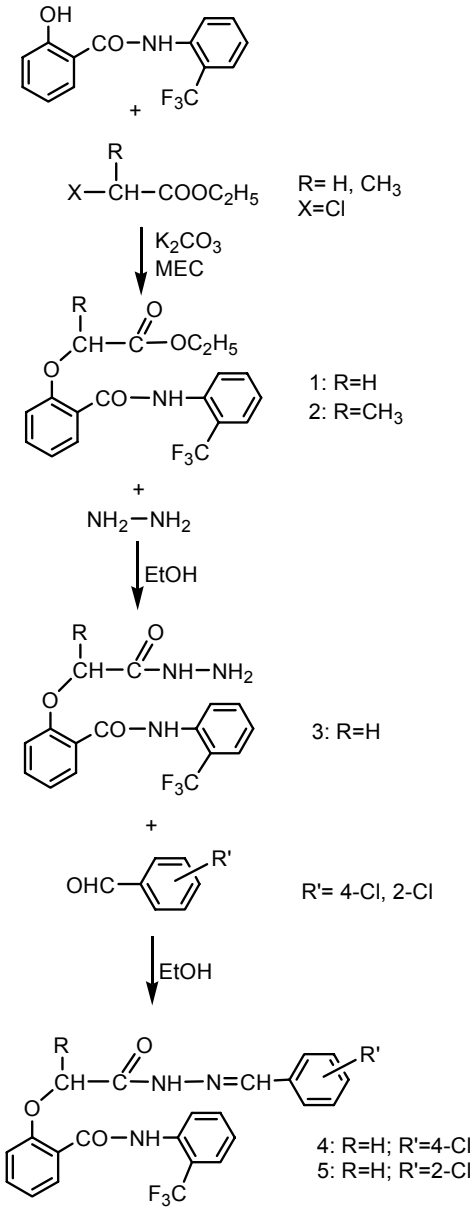
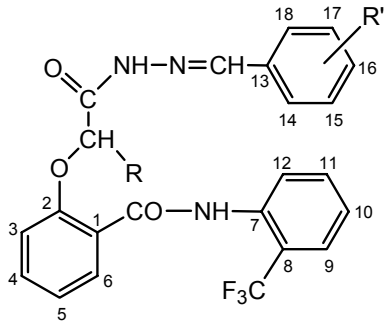


Scheme 1. The obtaining pathways of the synthesized compounds.



Scheme 2. Numbering of the aromatic rings.

Table 1

The synthesized compounds

Comp. no.	Compound name	R	R'	Molecular formula/ Weight
1	[2-(2-Trifluoromethyl-phenylcarbamoyl)-phenoxy]-acetic acid ethyl ester	H	-	$C_{18}H_{16}F_3NO_4$ 367.10
2	2-[2-(2-Trifluoromethyl-phenylcarbamoyl)-phenoxy]-propionic acid ethyl ester	CH_3	-	$C_{19}H_{18}F_3NO_4$ 381.12
3	2-Hydrazinocarbonylmethoxy-*N*-(2-trifluoromethyl-phenyl)-benzamide	H	-	$C_{16}H_{14}F_3N_3O_3$ 353.10
4	2-(4-Chloro-benzylidene-hydrazinocarbonylmethoxy)-*N*-(2-trifluoromethyl-phenyl)-benzamide	H	4-Cl	$C_{23}H_{17}ClF_3N_3O_3$ 475.09
5	2-(2-Chloro-benzylidene-hydrazinocarbonylmethoxy)-*N*-(2-trifluoromethyl-phenyl)-benzamide	H	2-Cl	$C_{23}H_{17}ClF_3N_3O_3$ 475.09

The synthesized compounds were also analyzed by ^{1}H-NMR in DMSO and ^{13}C-NMR in CCl_3. In order to facilitate the NMR data interpretation, in Scheme 2, the numbering of the aromatic rings is presented. The ^{1}H-NMR shifts of ethyl group from esters appear between 1.1-4.3 ppm, that of amidic group between 10.0-11.3 ppm, that of hydrazidic group, from both of, hydrazides and hydrazones, between 9.0-12.2 ppm, and that of iminic group between 8.4-8.7 ppm. The ^{13}C-NMR signals corresponding to both carbons from hydrazidic and amidic groups appear between 163-168 ppm and those for aromatic carbons between 115-156 ppm.

The characterization was completed with MS analysis, using positive electrospray ionization (+ESI) technique. The samples were dissolved in pure methanol, and both +MS^1 and tandem mass spectra +MS^n (n=2-6) were acquired. The MS^1 and mass calculation revealed the presence only of the peaks corresponding to the protonated and/or sodiated and potassiated molecular ions: $[M+H]^+$, $[M+Na]^+$ and $[M+K]^+$ while the fragmentation spectra unambiguously confirmed their structure.

A number of 5 novel compounds, 2-hydroxy-*N*-(2-trifluoromethyl-phenyl)-benzamide derivatives, were synthesized and characterized. The 1:1 molar ratio for reagents gave good yields (>68%) after final purification. The employed analytical methods prove the identity and provide the elemental composition of all investigated compounds.

EXPERIMENTAL

Reagents: ethyl chloroacetate, ethyl 2-chloropropionate (Aldrich, for synthesis); hydrazinium monohydrate ($N_2H_4 \cdot H_2O$) (Merck, for synthesis); 4-chlorobenzaldehyde, 2-chlorobenzaldehyde (Merck, for synthesis); 2-hydroxy-*N*-(2-trifluoromethyl-phenyl)-benzamide[9]; Solvents: absolute ethanol, ethyl-methylketone, dimethylformamide (Merck, analytical purity).

Melting points were determinated with a Böetius Carl-Zeiss Jena apparatus. IR spectra in KBr pellet were recorded on Jaskow FT/IR-430 apparatus and NMR spectra were recorded on "Bruker Avance DRX 400" instrument. Mass spectra were recorded on a high capacity ion trap, HCT Ultra PTM instrument (Bruker, Daltonics, Bremen), interfaced to a PC running the Compass^{TM} 1.2. integrated software package, which includes the Hystar^{TM} 3.2.37 module for instrument controlling and spectrum acquisition, Esquire Control^{TM} 6.1.512 and Data Analysis^{TM} 3.4.179 modules for storing the ion chromatograms and processing the MS data.

1. Synthesis of the ethyl esters **1-2**.[14] Ethyl esters were obtained by the reaction of 2-hydroxy-*N*-(2-trifluoromethyl-phenyl)-benzamide with ethyl α-halogenated acid esters in ethyl-methylketone medium. A mixture of 0.025 mol 2-hydroxy-*N*-(2-trifluoromethyl-phenyl)-benzamide obtained and purified according to reference **9**, and 0.025 mol anhydrous K_2CO_3 was refluxed in 120 mL ethyl-methylketone. Ethyl α-halogenated acid ester (0.025 mol) was added dropwise. Optimum molar ratio was amide: ester: K_2CO_3=1:1:1. The mixture was stirred and heated on a steam bath for 5 h. After cooling at room temperature, the mixture was poured into water, and shacked intensively. The organic phase was separated and dried over $MgSO_4$. After filtration and evaporation of solvent in vacuum, the esters were crystallized. The solid esters were recrystallized from ethanol.

2. Synthesis of the hydrazide **3**.[10] A mixture of [2-(2-trifluoromethyl-phenylcarbamoyl)-phenoxy]-acetic acid ethyl ester (0.015 mol) and hydrazine hydrate (6.6 mL) was refluxed in 50 mL ethanol for 3 h. The reaction mixture was cooled and the separated solid was filtered, and then recrystallized from ethanol.

3. Synthesis of the hydrazones **4,5**.[10] To a solution of 0.003 mol hydrazide in 30 mL ethanol, 0.003 mol of an appropriate benzaldehyde were added. The reaction mixture was refluxed for 5 h. The solid, obtained after cooling, was filtered off, washed with water and recrystallized from dimethylformamide.

Yields, uncorrected melting points and spectral data of these compounds are shown in Table 2.

Table 2

Synthesized compounds characteristics

Comp. no.	Yield (%)	M.p. (^{o}C)	Spectral data
1	78	107-110	**IR** ν(cm^{-1}): 3328m, 3066s, 1757i, 1666i, 1600m, 1550i, 1494m, 1456s, 1436s, 1392s, 1286m, 1224i, 1170i, 1122i, 1095m, 1043s, 1020s, 783s, 756m, 709m; **^{1}H-NMR** [δ(ppm)]: 1.23 (t, 3H, $COOCH_2\underline{CH_3}$); 4.24 (q, 2H, $COO\underline{CH_2}CH_3$); 5.00 (s, 2H, $O\underline{CH_2}CO$); 7.16 (t, 1H, H_{10}); 7.21 (d, 1H, H_3); 7.46 (d, 1H, H_5); 7.57 (t, 1H, H_{11}); 7.62 (t, 1H, H_4); 7.90 (d, 1H, H_9); 8.04 (d, 1H, H_{12}); 8.33 (s, 1H, H_6); 10.68 (s, 1H, CON$\underline{H}$); **^{13}C-NMR** [δ(ppm)]: 13.89 ($COOCH_2\underline{C}H_3$); 61.07 ($COO\underline{C}H_2CH_3$); 65.79 ($O\underline{C}H_2CO$); 113.57 (CF_3); 115.92 (C_3); 119.90 (C_1); 121.65 (C_{12}); 122.88 (C_5); 123.34 (C_8); 125.44 (C_{10}); 129.33 (C_9); 129.91 (C_6); 130.75 (C_{11}); 133.05 (C_4); 139.61 (C_7); 155.08 (C_2); 163.75 ($\underline{C}ONH$); 168.69 ($\underline{C}OOC_2H_5$); **(+)MS^1** (m/z): 390.1 ($[M+Na]^+$); 368.1 ($[M+H]^+$); **(+)MS^n** (m/z): 368.0; 238.9; 224.9; 206.9; 178.9; 150.9; 121.0;

2	68	80-85	**IR** ν(cm^{-1}): 3193m,l, 1720m, 1622i, 1595i, 1560i, 1498s, 1485s, 1456i, 1315i, 1269i, 1233i, 1218m, 1114i, 1103m, 1062m, 765m, 756m, 669m, 416s; **^{1}H-NMR** [δ(ppm)]: 1.11 (t, 3H, $COOCH_2C\underline{H_3}$); 1.61 (d, 3H, $OCH(C\underline{H_3})CO$); 4.13 (q, 2H, $COO\underline{CH_2}CH_3$); 5.39 (q, 1H, $OC\underline{H}(CH_3)CO$); 6.92 (t, 1H, H_{10}); 7.03 (d, 1H, H_3); 7.36-7.58 (m, 2H, H_5, H_{11}); 7.69-7.80 (m, 2H, H_4, H_9); 8.03 (dsc, 1H, H_{12}); 8.27 (d, 1H, H_6); 10.03 (s, 1H, CON<u>H</u>); **(+)MS^1** (m/z): 420.1 ($[M+K]^+$); 404.2 ($[M+Na]^+$); 382.2 ($[M+H]^+$); **(+)MS^n** (m/z): 382.1; 253.0 238.9; 220.9; 192.9; 164.9; 121.1;
3	94	184-186	**IR** ν(cm^{-1}): 3340m, 3288m, 3051s, 1662i, 1600m, 1558m, 1494m, 1450s, 1340i, 1288s, 1230i, 1164m, 1093s, 1072s, 1053s, 752s, 700s; **^{1}H-NMR** [δ(ppm)]: 4.44 (s, 2H, NH-$\underline{NH_2}$); 4.81 (s, 2H, $O\underline{CH_2}CO$); 7.16 (t, 1H, H_{10}); 7.26 (d, 1H, H_3); 7.45 (t, 1H, H_5); 7.55 (tsc, 1H, H_{11}); 7.60 (t, 1H, H_4); 7.82 (dsc, 1H, H_9); 8.00 (dsc, 1H, H_{12}); 8.40 (d, 1H, H_6); 9.08, 9.51 (2 isomers: *cis*, *trans*) (s, 1H, CON<u>H</u>-NH_2); 11.03, 11.59 (2 isomers: *cis*, *trans*) (s, 1H, CON<u>H</u>-Ar); **^{13}C-NMR** [δ(ppm)]: 66.75 ($O\underline{C}H_2CO$); 113.84 (CF_3); 115.70 (C_3); 119.86 (C_1); 121.80 (C_{12}); 123.32 (C_5); 124.02 (C_8); 125.46 (C_{10}); 129.64 (C_9); 129.92 (C_6); 130.66 (C_{11}); 132.90 (C_4); 139.78 (C_7); 155.23 (C_2); 164.33 (<u>C</u>ONH-Ar); 167.13 (<u>C</u>ONH-NH_2); **(+)MS^1** (m/z): 354.1 ($[M+H]^+$); **(+)MS^n** (m/z): 354.1; 282.0; 224.9; 210.9 192.9; 165.0; 121.1;
4	85	227-229	**IR** ν(cm^{-1}): 3300m, 3235m,l, 1705i, 1650i, 1594i, 1540i, 1480i, 1442i, 1268m, 1233m, 1077m, 816s, 732s, 694s; **^{1}H-NMR** [δ(ppm)]: 5.45 (s, 2H, $O\underline{CH_2}CO$); 7.19 (t, 1H, H_{10}); 7.39 (d, 1H, H_3); 7.46 (d, 1H, H_5); 7.53 (d, 2H, H_9, H_{12}); 7.61 (t, 2H, H_4, H_{11}); 7.82 (d, 2H, H_{15}, H_{17}); 8.04 (dsc, 2H, H_{14}, H_{18}); 8.22 (dsc, 1H, H_6); 8.40 (s, 1H, -N=<u>CH</u>-); 10.90, 11.28 (2 isomers: *cis*, *trans*) (s, 1H, CON<u>H</u>-Ar); 11.84, 12.02 (2 isomers: *cis*, *trans*) (s, 1H, CON<u>H</u>-N=CH-); **(+)MS^1** (m/z): 498.2 ($[M+Na]^+$); 476.1 ($[M+H]^+$); **(+)MS^n** (m/z): 476.1; 333.0; 315.0; 287.0;
5	87	169-170	**IR** ν(cm^{-1}): 3336m, 3224m,l, 3058s, 1720i, 1645i, 1593m, 1552m, 1473m, 1446m, 1257m, 1238i, 1062m, 800m, 752i, 727m, 715m, 686s, 542s, 507s, 410s; **^{1}H-NMR** [δ(ppm)]: 5.47 (s, 2H, $O\underline{CH_2}CO$); 7.19 (t, 1H, H_{10}); 7.24 (d, 1H, H_3); 7.37-7.63 (m, 4H, H_5, H_{11}, H_{17}, H_4); 7.86 (d, 1H, H_9); 8.04 (dsc, 1H, H_{15}); 8.12-8.15 (m, 1H, H_{16}); 8.22 (d, 1H, H_{12}); 8.38 (d, 1H, H_{18}); 8.46 (s, 1H, H_6); 8.66 (s, 1H, -N=<u>CH</u>-); 10.86, 11.25 (2 isomers: *cis*, *trans*) (s, 1H, CON<u>H</u>-Ar); 12.03, 12.13 (2 isomers: *cis*, *trans*) (s, 1H, CON<u>H</u>-N=CH-); **(+)MS^1** (m/z): 498.2 ($[M+Na]^+$); 476.1 ($[M+H]^+$); **(+)MS^n** (m/z): 476.1; 333.0; 315.0; 287.0; 216.9; 177.9; 121.0;

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