Microwave - assisted Synthesis of 2-*p*-Amino-Salicyloxyacetanilides

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Ten substituted 2-p-aminosalicyloxyacetanilide by condensation of sodium salt of the p-aminosalicylic acid with several chloroacetanilides under the microwaves action. Within the electronic spectra there are wide absorption bands (from 280 to 320 nm) as result of the extended conjugation of the chromophores on the whole molecule after condensation of raw materials. The new compounds present the potential photoprotective action. The molecular structure of these compounds was established by UV, IR absorption and ^{1}H-NMR spectra.

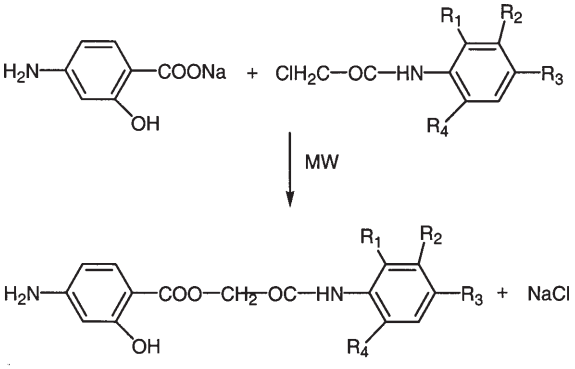
Keywords: photoprotection, 2-p-amino-salicyloxyacetanilides, microwave assisted reaction

Skin ageing and the frequency of skin cancer are on the rise. Responsible for this is solar radiation within the 290-390 nm band, which is called UV-B, and the radiation in the 320-400 nm band, which is called UV-A. For protection against solar radiation there are solar filters, organic compounds within the UV-A scale and solar panels, and in particular Zinc dioxide and Titanium dioxide for the UV-A scale, which absorb or entirely reflect solar radiation. Solar filters are not very often used for this purpose as they should resort to colourful compounds that absorb in the visible, but cause stains. [1, 2]

This research suggests synthesizing some esteramides obtained by condensation of sodium salts of the *p*-aminosalicylic acid (used in therapeutics) with chloroacetanilides (used for obtaining local anaesthetics such as lidocain) [3, 4].

While knowing the absorption bands in UV of the *p*-aminosalicylic acid and of acetanilides, we expected that the new esteramides have a wider absorption band in order to cover not only the UV-B domain, but also part of the UV-A. [5, 6].

For the synthesis of esteramides we chose the condensation of sodium salt of the *p*-aminosalicylic acid with differently substituted chloracetanilides [7].



where, R_1, R_2, R_3, R_4 can be: H, CH_3, C_2H_5, Cl, NO_2, OCH_3

The reaction is activated by microwaves. After 60 seconds, only 30% of the reaction takes place, according to the HPLC checking. That is why, in order to complete it, the reaction time was extended to 6 minutes, which is 20 times as short as the time needed in classical conditions. On the other hand, pure compounds result from the reaction.

Experimental part

The 2-chloroacetanilides were prepared according to the reference material.

The sodiumaminosalicylate, a Merck product, was not purified.

The analysis of C, H and N was done by micro-combustion while using a Perkin-Elmer 2400 CHN automatic analyzer.

The melting points (*mp*) were determined with a Boetius apparatus and are not corrected.

Electronic spectra were obtained with Specord 40 spectrometer in ethanol solution, 10^{-5} M.

IR spectra were recorded within 4000-400 cm^{-1} range by BRUKER VERTEX 70 Fourier transform infrared spectrometer in KBr pellets.

^{1}H-NMR spectra were recorded on a Varian EM-360 spectrometer operating in $CDCl_3$ and DMSO-d_6. The chemical shifts were referred to TMS as internal standard.

All ten new compounds were synthesized in the following example after several attempts of classical synthesis by infrared heating for 20 h. When using a monomode Initiator microwave oven, we noticed that the synthesis reaction happened very fast after reaching 130 Centigrade degrees, in DMSO solvent, without pressure rise. The whole process was based on a very high energy level which equals 400 Watt.

4-Amino-2-hydroxibenzoic-phenylcarbamoil, methyl ester

A total of 0.169 g 2-chloroacetanilide (1mmol), 0.175 g sodiumaminosalicylate (1 mmol) were added to 1 mL DMSO in a thick-walled reaction tube, under magnetic stirring. The respective tube was hermetically closed, and the initiator was programmed to 130 Centigrade , degrees for 6 min , and to 60 s of pre-stirring. On reaching the respective temperature, the magnetron produced with MW irradiation. Then the reaction tube was left to cool and when it reached 50 degrees Centigrade, the apparatus set it free. The tube was opened with the help of tongs and the reaction mass was poured into a 80 mL Berzelius glass with cooled water, under magnetic stirring. A white precipitate was formed which was filtered under low pressure and it was washed several times with water on the filter.

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Table 1
ANALYTICAL DATA

No.	Compound R_1 R_2 R_3 R_4	Formula	Molecular mass	Yield (%)	*mp* (^{0}C)	λ_{max} (nm)
1	H H H H	$C_{15}H_{14}N_2O_4$	286.2836	57.43	184-6	280-320
2	Me H H H	$C_{16}H_{16}N_2O_4$	300.3104	71.42	228	280-320
3	H Me H H	$C_{16}H_{16}N_2O_4$	300.3104	31.28	212	280-320
4	H H Me H	$C_{16}H_{16}N_2O_4$	300.3104	71.00	230	270-320
5	Me H H Me	$C_{17}H_{18}N_2O_4$	314.3189	59.85	243	280-320
6	H H Et H	$C_{17}H_{18}N_2O_4$	314.3189	53.47	161.5	280-320
7	H H Cl H	$C_{15}H_{13}ClN_2O_4$	320.7277	66.74	193	280-320
8	Cl H Cl H	$C_{15}H_{12}Cl_2N_2O_4$	355.1738	82.35	194	low absorption
9	Cl H H Cl	$C_{15}H_{12}Cl_2N_2O_4$	355.1738	78.69	225	low absorption
10	H H NO_2 H	$C_{15}H_{13}N_3O_6$	331.2501	54.46	195	280-320

Table 2
ELEMENTAL ANALYSIS

No.	Compound R_1 R_2 R_3 R_4	Formula	Molecular mass g/moles	% C calc. / found	% H calc. / found	% N calc. / found
1	H H H H	$C_{15}H_{14}N_2O_4$	286.28	62.93 / 62.99	4.93 / 5.24	9.78 / 10.09
2	Me H H H	$C_{16}H_{16}N_2O_4$	300.31	63.99 / 64.32	5.37 / 5.62	9.33 / 8.92
3	H Me H H	$C_{16}H_{16}N_2O_4$	300.31	63.99 / 63.78	5.37 / 5.58	9.33 / 9.43
4	H H Me H	$C_{16}H_{16}N_2O_4$	300.31	63.99 / 63.61	5.37 / 5.61	9.33 / 9.16
5	Me H H Me	$C_{17}H_{18}N_2O_4$	314.31	64.96 / 64.68	5.77 / 5.76	8.91 / 9.08
6	H H Et H	$C_{17}H_{18}N_2O_4$	314.31	64.96 / 64.70	5.77 / 5.90	8.91 / 9.23
7	H H Cl H	$C_{15}H_{13}ClN_2O_4$	320.72	51.40 / 51.08	3.22 / 3.61	8.59 / 7.94
8	Cl H Cl H	$C_{15}H_{12}Cl_2N_2O_4$	355.17	50.72 / 51.10	3.41 / 3.76	7.89 / 7.51
9	Cl H H Cl	$C_{15}H_{12}Cl_2N_2O_4$	355.17	50.72 / 50.37	3.41 / 3.21	7.89 / 8.25
10	H H NO_2 H	$C_{15}H_{13}N_3O_6$	331.25	54.38 / 54.74	3.96 / 4.36	12.68 / 12.68

After drying, the Beilstein test was negative which indicated the lack of organically tight chlorine.

0.164 grams of product resulted. Efficiency: 57.48%. Melting point: 185-186 degrees Centigrade.

Results and Discussions

Treatment of 2-cloroacetanilide and its derivatives with sodiumaminosalicylate under microwave irradiation in DMSO gave ten new compounds, 2-*p*-amino-salicyloxy-acetanilides.

Some properties are shown in table 1.

Efficiency overcomes 50% and depends on the molecular structure of the compounds.

All the compounds are solid, crystallized and colourless.

Within the electronic spectra there are wide absorption bands (from 280 to 320 nm) as result of the extended conjugation of the chromophores on the whole molecule after condensation of raw materials.

In table 2 are shown the results of the elemental analysis (C, H, N) with values of +/- 0.4% by comparison with the calculated ones.

The IR spectrum (table 3) recorded in KBr pellets reflects the molecular structure of the new compounds. The band characteristics of the secondary amides (ν_{N-H}) appear within the 3365-3447 cm^{-1} range. The very strong amide band I ($\nu_{C=O}$) appears within the 1645-1627 cm^{-1}. The stretch of $\nu_{C=O}$ of esters occurs at 1697-1663 cm^{-1}.

^{1}H-NMR spectra (Table 4) recorded in the $CDCl_3$ and DMSO-d_6 solution support the structure formulas assigned to these compounds.

No.	ν_{N-H}	ν_{NH2}	ν_{Ar-H}	ν_{CH3as} / ν_{CH3s}	$\nu_{C=O}$ Amide I	ν_{COOR} ester	$\nu_{C=C}$	δ_{NH}	$\nu_{C-O-Cas}$ / ν_{C-O-Cs}
1	3428	3269	3096	2964	1627	1667	1599	1538	1160
			3061	2872					1111
2		3267	3096	2948	1627	1667	1599	1538	1160
			3059	2865					1111
3	3406	3311	3105	2950	1627	1673	1595	1548	1162
			3051	2861					1114
4		3274	3090	2949	1614	1667		1538	1160
			3065	2865					1111
5	3384	3246	3040	2958	1636	1667	1540	1541	1158
				2856					1111
6	3365	3275	3064	2963	1664	1697	1575	1541	1157
			3033	2872					1102
7	3447	3276	3065	2952	1630	1659	1596	1546	1155
			2948	2864					1116
8	3885	3265	3081	2951	1636	1671	1557	1557	1157
			3004						1096
9	3371	3260	3094	2934	1591	1676	1591	1523	1155
			3048	2875					1027
10	3467	3214	3090	2923	1645	1667	1594	1537	1148
			3036	2853					1118

Table 3
FTIR SPECTRA

No.	Compound R_1 R_2 R_3 R_4	δ (ppm)
1	H H H H	9.29s(1H); 7.44m(8H); 6.03s(1H); 4.78s (2H); 3.50s (2H);
2	Me H H H	9.16s(1H); 7.10m(6H); 6.04s(1H); 5.39s (1H); 4.73s (2H); 2.23s(3H)
3	H Me H H	9.72s(1H); 7.13m(7H); 6.2s(1H); 4.92s(2H); 3.85s(2H); 2.41s(3H)
4	H H Me H	9.42s(1H); 7.51m(7H); 6.15s(1H), 4.83s(2H); 3.30s(2H); 2.37s(3H)
5	Me H H Me	9.18s(1H); 7.05s(6H); 6.13s(1H); 4.86s(2H); 3.36s(2H); 2.17s(6H)
6	H H Et H	6.46s(1H); 7.46m(7H); 6.71s(1H); 4.83s(2H); 4.26s(2H); 2.72c(2H); 1.33t(3H)
7	H H Cl H	9.81s(1H); 7.70s(3H); 6.13s(1H); 4.85s(2H); 3.84s(2H);
8	Cl H Cl H	9.78s(1H); 7.32m(6H); 6.93s(1H); 4.89s(2H); 3.66s(2H);
9	Cl H H Cl	9.72s(1H); 7.,49s(3H), 6.51m(3H); 5.16s(2H); 4.30s(1H); 3.58s(2H)
10	H H NO_2 H	9.68s(1H); 7.78m(7H); 6.10s(1H); 4.86s(2H); 3.63s(2H)

Table 4
1H-NMR DATA, δ(ppm)

Conclusions

In order to obtain compounds that act against solar radiation within the UV domain, we started from the hypothesis that this is possible with the help of UV absorption by using non-toxic compounds (frequently met in therapeutics) as raw materials.

By condensation reaction under microwaves action of PAS (sodium salts *p*-aminosalicylic acid), used in tuberculosis therapy, and chloroacetanilides (reagents for anaesthetic products synthesis, such as lidocaine) resulted esteramides which - due to the extended conjugation in the whole molecule –its have a wider absorption band than that of the raw materials in the UV-B domain.

These results confirmed our research assumption.

This subject was also approached by other researchers [8].

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