Microwave Assisted Synthesis of New Phenoxyacetalides Bearing Anaesthetic Properties

KAFAF BURHAN*
[1] University of Sulaimania, Department of Basic Sciences, Kurdistan Region

Eight 4-methylphenoxyacetoanilides were synthesized by o-alkylation of p-cresol with several 2-chloroacetanilides under microwave irradiation. The new compounds were characterized by elemental chemical analysis, UV-Vis, IR, MS and ^{1}H NMR spectra and may possess a local anaesthetic and antiarrhythmic activity.

Keywords: phenoxyacetoanilides, local anaesthetics, microwave irradiation

Löfgren and coworkers [1-3] reported synthesis of a high number of aminoacetanilides, among which lidocaine (2-diethylamino-*N*-2',6'-dimethylacetoxylidine) that became soon a local anaesthetic drug. By replacing the diethylamino group with perhydroazepin group, a new compound called pincainide was obtained bearing important anaesthetic and antiarrhythmic properties [4].

Both aminoacetaanilides, including pincainide and some phenoxy-2,6-dimethylacetanilides were screened for anaesthetic and antifibrillant activity [5].

The phenoxyacetanilides were prepared by condensation of chloroacetyl-2,6-xilidine with sodium phenoxides. The phenoxides resulted from the reaction of phenols with sodium hydroxide and were isolated following an original methodology in order to remove the resulted water: azeotrope distillation of the ternary azeotrope mixture formed by water-ethanol-benzene (fig.1) [6].

The phenoxides resulted from the reaction of phenols with sodium hydroxide and were isolated following an original methodology in order to remove the resulted water: azeotrope distillation of the ternary azeotrope mixture formed by water-ethanol-benzene (fig.1) [6].

Pharmacological studies on laboratory animals showed that 2,6-dimethyl-phenoxyacetanilides have a lower local anaesthetic activity than the reference compounds (cocaine, procaine, lidocaine). However, they bear a higher antifibrillant activity than xyline [5]. Moreover, it was shown that the presence of a methyl group in position 4 of the phenoxide ring increased the antifibrillant properties.

Therefore, we sought to synthesize some new 4-methylphenoxyacetoanilides that bear different substituents on the anilide moiety (fig. 2).

Experimental part

p-Cresol was purchased from Merck. The 2-chloro-acetanilides were synthesized as previously described [1-3].

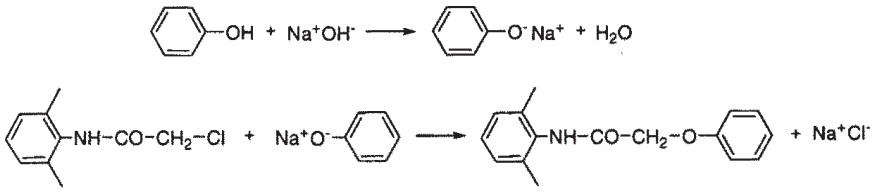


Fig.1. Synthesis of phenoxyacetanilides

Microanalysis was performed using a Perkin-Elmer 2400 CHN analyzer. The chromatographic analysis was performed on a HPLC CECIL CE 4900 equipment, using an ODS 25 cm column and a mixture of MeOH/water (1:1, v/v) as mobile phase, at a flow of 1 mL/min.

Melting points were determined using an electric melting point Boetius apparatus and are uncorrected.

The electronic spectra were recorded on a Specord 40 spectrophotometer in the range 200-800 nm, using ethanol as solvent, at a concentration of 10^{-4} M.

The IR spectra were recorded on a Biorad FTS-135 Spectrometer in KBr pellets in the range of 4000-400 cm^{-1}.

A Varian EM 360 spectrometer was used for ^{1}H NMR recordings using DMSO-d_6 or/and $CDCl_3$ as solvents. Chemical shifts (δ) are reported in parts per million values using TMS as internal reference.

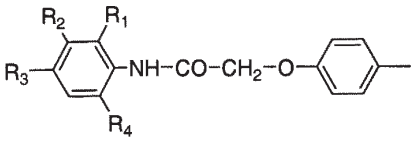
Molecular weight was obtained with a GC MS 8000 MD 800 Fissions spectrometer at 70 eV, carrier gas He at 2 mL/min.

Some of phenols react with primary alkyl halides in presence of sodium amide or sodium hydride under microwave irradiation to yield aromatic ethers.

There have been reported few synthetic procedures for the conversion of phenols into aromatic ethers without previous formation of the corresponding phenoxides [8]. One such case was reported [8], where there were used catalytic amounts of tetra-*n*-butylammonium bromide (TBAB) and alkyl halide in 50% excess to prepare aromatic ethers, under anhydrous conditions, in presence of microwave radiations [7].

Herein, we report a simple procedure for the synthesis of aromatic ethers, which occurs under mild conditions, in short times, using inexpensive reagents and no catalyst.

The new compounds were synthesized as described for 4-methyl-phenoxy-2',6'-dimethylacetanilide: *p*-cresol (0.216, 2 mmol), 2',6'-dimethyl-2-chloro acetanilide (0.395



where R^1,R^2, R^4= H, CH_3, C_2H_5, Cl, OMe
R^3= H, CH_3, C_2H_5, *i*Pr, Cl

Fig.2. Structures of the new 4-methylphenoxyacetoanilides

* email: soccer_team1@yahoo.com

No.	Compound				Formula	Molec. weight	Calc. (%)			Found (%)		
	R^1	R^2	R^3	R^4			C	H	N	C	H	N
1	H	H	H	H	$C_{15}H_{15}NO_2$	241.28	74.67	6.27	5.81	74.38	6.14	6.32
2	Me	H	H	H	$C_{16}H_{17}NO_2$	255.31	74.27	6.71	5.49	74.63	6.42	5.21
3	H	Me	H	H	$C_{16}H_{17}NO_2$	255.31	74.27	6.71	5.49	74.66	6.75	5.22
4	H	H	Me	H	$C_{16}H_{17}NO_2$	255.31	74.27	6.71	5.49	74.58	6.36	5.30
5	H	H	Et	H	$C_{16}H_{19}NO_2$	269.34	75.81	7.11	5.20	75.94	6.76	5.08
6	H	Me	H	Me	$C_{16}H_{19}NO_2$	269.34	75.81	7.11	5.20	75.57	6.87	5.46
7	Me	H	H	Me	$C_{16}H_{19}NO_2$	269.34	75.81	7.11	5.20	75.48	6.92	5.01
8	H	H	*i*Pr	H	$C_{18}H_{21}NO_2$	283.36	76.29	7.47	4.94	76.21	7.38	5.19

Table 1
ELEMENTAL ANALYSES

Table 2
YIELDS AND MELTING POINTS

No.	Compound				η (%)	mp (°C)
	R^1	R^2	R^3	R^4		
1	H	H	H	H	78.13	104
2	Me	H	H	H	76.78	114
3	H	Me	H	H	71.84	129
4	H	H	Me	H	69.73	99,5
5	H	H	Et	H	68.92	98
6	H	Me	H	Me	83.93	123
7	Me	H	H	Me	83.42	114
8	H	H	*i*Pr	H	94.12	80.5

g, 2 mmol) and NaOH (0.08 g, 2 mmol) were dissolved in 1 mL of DMSO under stirring, in a microwave vial. The vial was closed tight and subjected to microwave irradiation. The temperature was set at 130°C for 7 min, at very high level of absorption.

The irradiation started after the temperature reached the set value. After 7 min , the irradiation stopped and the temperature was left to reach 50°C before taking out the reaction vial. The vial was then opened and the reaction mixture was poured into cold water, under vigorous stirring. The white precipitate that formed was washed several times with water on a Buchner funnel and allowed to dry. The resulted solid weighted 0.453 g (83.42%) and had a melting point of 114°C. Negative Beilstein sample that was performed indicated that the reaction was complete. Moreover, HPLC analysis confirmed the purity of the compound.

Results and discussions

Treatment of 2-chloroacetanilide and its substituted derivatives with p-cresol and sodium hydroxide, under

No.	Compound				NH	C_{Ar}-H	$CH_{3\,es}$ / $CH_{3\,s}$	C=O	C=C	C-O-C_{as} / C-O-C_s	C-H
	R^1	R^2	R^3	R^4							
1	H	H	H	H	3408	3077 3099	2951 2859	1695	1594 1507	1227 1069	812
2	Me	H	H	H	3375	3057 3053	2910 2838	1684	1597 1506	1239 1066	810
3	H	Me	H	H	3328	3066 3030	2956 2859	1670	1595 1508	1235 1060	815
4	H	H	Me	H	3351	3060 3028	2918 2855	1674	1594 1509	1242 1071	824
5	H	H	Et	H	3367	3032	2962 2868	1683	1594 1500	1240 1066	827
6	H	Me	H	Me	3355	3024	2975 2872	1676	1577 1509	1246 1060	812
7	Me	H	H	Me	3275	3034	2961 2856	1669	1509	1248 1062	821
8	H	H	*i*Pr	H	3316	3080 3033	2958 2868	1673	1613 1514	1249 1054	826

Table 3
FTIR SPECTRA, ν, cm^{-1}

No.	Compound				δ (ppm)
	R^1	R^2	R^3	R^4	
1	H	H	H	H	8.18 (s, 1H), 7.10 (m, 9H), 4.43 (s, 2H), 2.23 (s, 3H)
2	Me	H	H	H	8.19 (s, 1H), 7.16 (m, 8H), 4.56 (s, 2H), 2.26 (s, 6H)
3	H	Me	H	H	8.29 (s, 1H), 7.03 (m, 8H), 4.45 (s, 2H), 2.23 (s, 6H)
4	H	H	Me	H	8.36 (s, 1H), 7.16 (m, 8H), 4.50(s, 2H), 2.23 (s, 6H)
5	H	H	Et	H	8.56 (s, 1H), 7.00 (m, 8H), 4.42 (s, 2H), 2.63 (q, 2H), 2.23 (s, 6H), 1.08 (t, 3H)
6	H	Me	H	Me	7.83(s 1H), 7.07 (m, 7H), 4.66 (s, 2H), 2.21(s, 3H), 2.10 (s, 6H)
7	Me	H	H	Me	.28 (s, 1H), 7.06 (m, 7H), 4.66 (s, 2H), 2.26 (s, 6H), 2.23 (s, 6H)
8	H	H	*i*Pr	H	8.28 (s, 1H), 7.21 (m, 8H), 4.53 (s, 2H), 4.15 (s, 1H), 2.20 (s, 3H), 1.41 (s, 6H)

Table 4
NMR DATA

microwave irradiation, in DMSO, yielded eight new ethoxy-amides derivatives with potential biological activity.

Table 1 shows the elemental analysis data which confirm structure of the compounds.

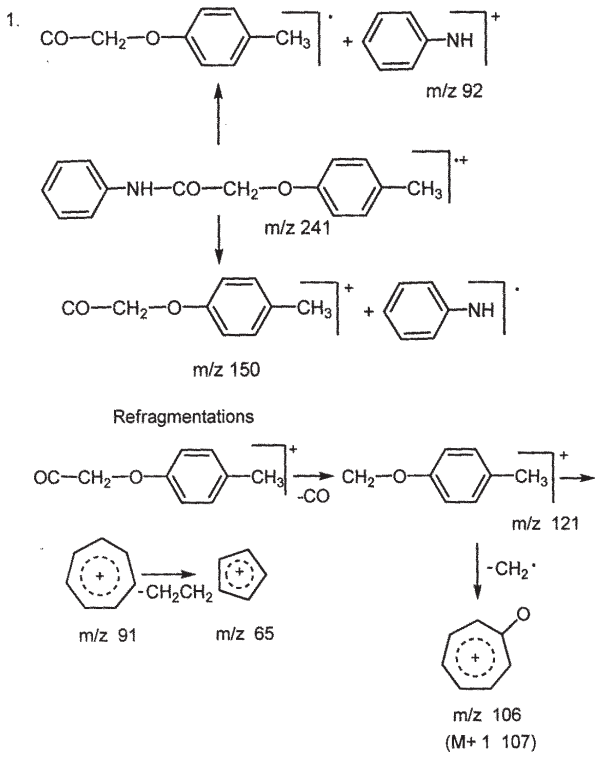
All compounds are colorless, crystalline solids having melting points around 100°C (table 2).

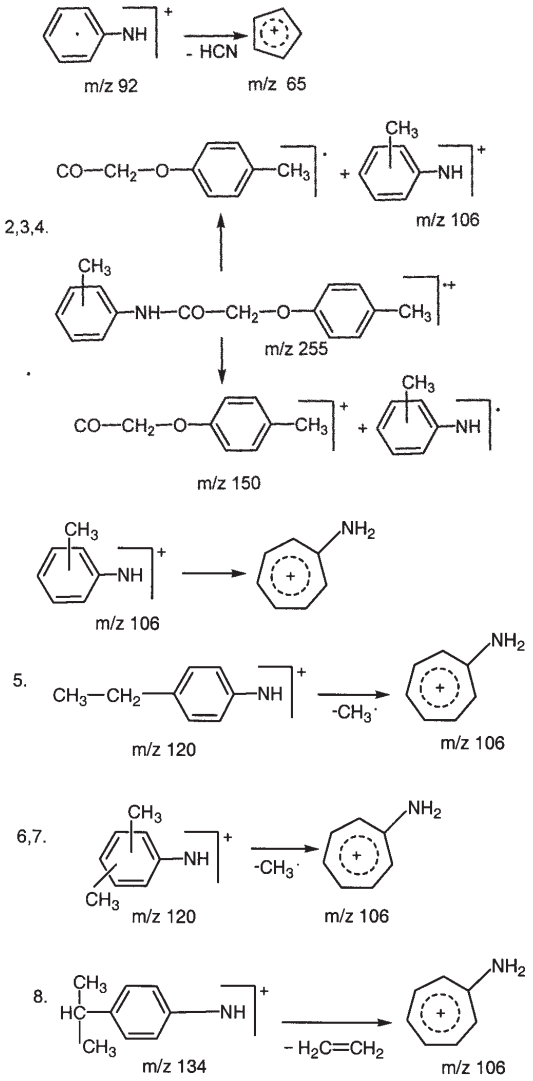
The reactions occurred in good yields, varying between 69 and 94%.Each group component was characterized by IR absorption spectra (table 3).

The ^{1}H NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ and confirm the molecular structures of the new synthesized compounds.

Fragmentation processes can support the structures formulas assigned to the compounds. The fragmentation process specific to the aromatic amides occurring by the cleavage of the bond between the N and C atoms of the carbonyl group followed by CO elimination.

Fragmentation of ions





In all mass spectra of phenoxy acetanilides, the peaks base and the peaks of molecular ions are the same.

Conclusions

In summary, condensation of 2-chloroacetanilides with *p*-cresol and sodium hydroxide could be easily achieved under microwave irradiation. The appropriate solvent proved to be dimethylsulfoxide. The reaction efficiently occurred in a very short time (7 min) and isolation of the product consisted of simple precipitation from water. The impurities were soluble in water and the products required no further purifications.

References

1. LÖFGREN, N. FISCHER, J., Swenska, Kem. Tid. **58**, 1946, pp.58; CA 43, 1023d; 1949
2. LÖFGREN, N., Arkiv, Kemi, Mineral Geol A **22**, No 18, 1940, pp. CA 43, 1021f; 1949
3. LÖFGREN, N., LIUNDQUIST,B., Swenska, Kem. Tid. **58**, 1946, pp.206; CA 43, 1022d; 1949
4. MURGU, L., DOBRESCU, D., DROE,G., BRALOSTINTEANU, L., STOICESCU, V., IOVU, M., Farmacia, **XXXVIII**, No. 3-4, p. 1990
5. IOVU, M., MURGU, L., BURA, C., GHEORGHISOR,M., Farmacia, **33**, no. 7, pp. 601-604, 1982
6. IOVU, M., ISPAS,F., Brevet Rom., 78807, 1982
7. BOSE, A.K., and al., J. Org. Chem, **56**, 6698, 1991
8. BOGDAL, D., OIELICHOWSKI,J., BORON, A., First International Electronic Conference on Synthetic Organic Chemistry, September 1997, p. 1

Manuscript received: 9.07.2009