Synthesis and Antimicrobial Activity of New Aromatic Esters of Potential Interest in Supramolecular Chemistry

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Herein we report a feasible study concerning syntheses, structure and biological activity of some new bisesters derived from benzenediols: pyrocatechol (1,2-), resorcine (1,3-), and hydroquinone (1,4-). Synthesis has been done both under classical heating and microwave irradiation. The microwave enhanced a remarkable rate of acceleration for esterification reaction (the reaction time decreasing dramatically), the yields are higher, the reaction conditions are milder, the consumed energy decreases considerably and the amount of used solvents is reduced substantially. Consequently, the microwave assisted esterification reaction could be considered eco-friendly. Antimicrobial tests prove that some esters compounds have a good activity against different microorganisms (germs and fungi). Correlations between structure and antimicrobial activity are reported.

Keywords: aromatic esters, phenols, microwave, synthesis, antimicrobial activity.

Aromatic bisesters are one of the most used classes of building blocks in supramolecular chemistry [1-3]. In the same time it was proved that some bisesters could have variously biological activity such us antimicrobial [4, 5], anticancer [6, 7], anesthesic [8, 9], etc. Recently published comprehensive books [10, 11] and papers [12-15] indicate that microwave (MW) irradiation has became an increasingly valuable tool in organic chemistry, since it offers a versatile and facile pathway in a large variety of syntheses. Thus, a large number of organic reactions can be carried out under MW irradiation in higher yields, shorter reaction time and milder conditions. Under classical heating esterification reaction of aromatic diols with chloroacyl chloride was extremely poorly studied, only in the case of benzene 1,2-diol with 2-chloroethanoyl chloride [16]. Moreover, under MW irradiation these sorts of reactions were not performed.

The emphasis of this work was to synthetise through conventional and nonconventional methods new aromatic bisesters of potential interest as building blocks in supramolecular chemistry and, to test their antimicrobial activity.

Experimental part

Syntheses of aromatic bisesters have been done under classical heating as well as under MW irradiation. All the reagents and solvents employed were of the best grade available and were used without further purification. Melting points were determined using an electrothermal apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra, and two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) were recorded on a Bruker Avance 400 DRX spectrometer operating at 400 MHz. The IR spectra were recorded on a FTIR Shimadzu Prestige 8400s spectrophotometer.

General procedure for syntheses of aromatic bisesters under classical heating

To 10 mmoles of benzenediols and 10 mmoles (2.43 g) of magnesium curlings in 50 mL anhydrous benzene, chloroacyl chloride (22 mmoles) it is added dropwise in 1 hour while stirring and refluxing the mixture and, it is continued to be refluxed for a period of 15 to 56 h (according with the reagents nature, table 1). The excess of magnesium were filtered off, the resulted oil is poured into water and, the precipitate formed filtered. The product was crystallized from an appropriate solvent. When the oil doesn't precipitate in water, first it was separated by flash than crystallized.

General procedure for syntheses of aromatic bisesters under MW irradiation

MW assisted reactions were carried out using a monomod reactor (STAR-2, CHEM corporation, USA). Using MW irradiation, the best results were obtained using a constant irradiation power (25% from the full power of the magnetron, 800 W) and varying the temperature (the so-called "power control"). The experimental device used for MW irradiation is presented in figure 1.

To 10 mmoles of benzenediols and 24 mmoles (24.24 g) triethylamine in 10 mL anhydrous benzene was placed in the reaction vessel (Pyrex glass or quartz). Chloroacyl

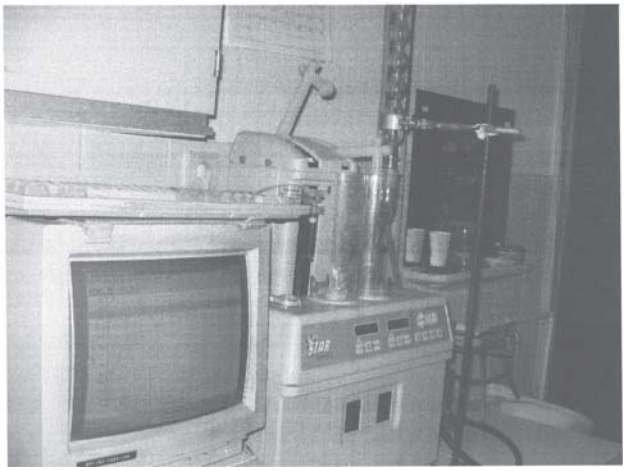

Fig. 1. The monomod microwave reactor STAR-2 for MW synthesis

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chloride (22 mmoles) it is added dropwise in 3-5 min. The tube is then placed in the microwave cell and heated for the appropriate time. Once the heating cycle is complete and tube was cooled to ambient temperature, the tube removed, and the triethyamine chlorohidrat was filtered off. The resulted oil is poured into water and, the precipitate formed filtered. The product was crystallized from an appropriate solvent. When the oil doesn't precipitate in water, first it was separated by flash then crystallized.

Microbiology

Antibacterial and antifungal activities of the compounds were determined by using diffusion technique on agar [17]. The bacteria and fungi were maintained on nutrient Mueller Hinton agar (Oxoid). The agar media were incubated with different microorganisms culture tested. After 24 h of incubation at 30°C for bacteria and 48 h of incubation at 28°C for fungi, the diameter of inhibition zone (mm) was measured (table 2). Chloramphenicol and nysatin were purchased from the market and used in a concentration of 30 mcg/disc and 100 mcg/disc respectively, as references for antibacterial and antifungal activities. The concentration of the new compounds was accordingly, 30 mcg/disc for bacteria and 100 mcg/disc for fungus *Candida*.

Chloro-acetic acid 2-(2chloro-acetoxy)-phenyl ester, 4. This compound was obtained from pyrocatechol, as white crystals, m.p.= 54-56°C. Anal. calc. for $C_{10}H_8Cl_2O_4$ (263): C 45.66, H 3.07; found: C 45.58, H 3.00. **IR (KBr, cm^{-1}):** 3016 (C-H arom.), 2975 (C-H alif.), 1782, 1751 (C=O est.), 1601, 1515, 1491, 1416 (C=C), 1248, 1128 (C-O-C), 814, 761 (C-Cl). **^{1}H-NMR ($CDCl_3$, δ, ppm, J, Hz):** 4.33 (s, 4H: $2H_{2'}$, $2H_{2''}$), 7.27–7.24 (m, 2H (overlaped peaks): $1H_4$, $1H_5$), 7.33–7.30 (m, 2H (overlaped peaks): $1H_3$, $1H_6$). **^{13}C-NMR (TMS, $CDCl_3$, δ, ppm):** 43.77 ($C_{2'}$, $C_{2''}$), 123.45 (C_3, C_6), 126.83 (C_4, C_5), 141.88 (C_1, C_2), 169.01 ($C_{1'}$, $C_{1''}$ ceto-est.).

Chloro-acetic acid 3-(2chloro-acetoxy)-phenyl ester, 7. This compound was obtained from resorcine, as redish crystals, m.p.= 66-68°C. Anal. calc. for $C_{10}H_8Cl_2O_4$ (263): C 45.66, H 3.07; found: C 45.57, H 3.02. **IR (KBr, cm^{-1}):** 3090 (C-H arom.), 2954 (C-H alif.), 1766, (C=O est.), 1593, 1544, 1481, 1406 (C=C), 1234, 1182, 1141 (C-O-C), 785 (C-Cl). **^{1}H-NMR ($CDCl_3$, δ, ppm, J, Hz):** 4.28 (s, 4H: $2H_{2'}$, $2H_{2''}$), 7.02 (s, 1H: H_2), 7.08–7.06 (d, 2H: $1H_4$, H_6), $J_{4,5(6,5)}$= 8.4), 7.43–7.39 (t, 1H: H_5, $J_{5,4(5,6)}$=8.4). **^{13}C-NMR (TMS, $CDCl_3$, δ, ppm):** 40.78 ($C_{2'}$, $C_{2''}$), 114.77 (C_2), 119.18 (C_4, C_6), 130.13 (C_5), 150.71 (C_1, C_3), 165.47 ($C_{1'}$, $C_{1''}$ ceto-est.).

Chloro-acetic acid 4-(2chloro-acetoxy)-phenyl ester, 10. This compound was obtained from hydroquinone, as white crystals, m.p.= 122-123°C. Anal. calc. for $C_{10}H_8Cl_2O_4$ (263): C 45.66, H 3.07; found: C 45.60, H 3.02. **IR (KBr, cm^{-1}):** 3003 (C-H arom.), 2953 (C-H alif.), 1770, 1761 (C=O est.), 1506, 1409, 1311 (C=C), 1188, 1232, 1146 (C-O-C), 736 (C-Cl). **^{1}H-NMR ($CDCl_3$, δ, ppm, J, Hz):** 4.30 (s, 4H: $2H_{2'}$, $2H_{2''}$), 7.17 (s, 4H: H_2, H_3, H_5 H_6). **^{13}C-NMR (TMS, $CDCl_3$, δ, ppm):** 40.98 ($C_{2'}$, $C_{2''}$), 122.45 (C_2, C_3, C_5, C_6), 148.20 (C_1, C_4), 165.39 ($C_{1'}$, $C_{1''}$ ceto-est.).

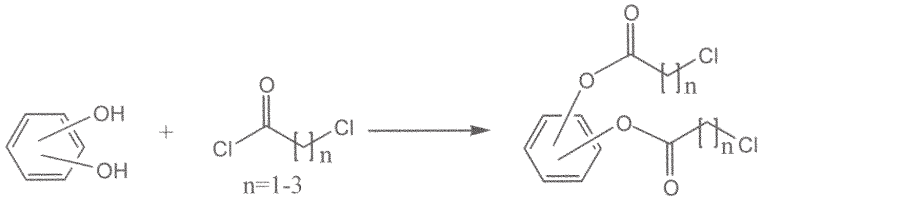
Results and discussion

In order to obtain the phenyl bisesters, we perform the esterification reaction of benzenediols (1,2-; 1,3- and 1,4-) with chloroacyl chloride (2-chloroethanoyl chloride, 3-chloropropanoyl chloride, 4-chlorobutanoyl chloride), scheme 2.

The reaction was carried out both under classical heating when catalyst was used magnesium curlings and, under MW irradiation when catalyst was used triethylamine. Under classical heating, the reactions pathways have some major disadvantages: long reaction time (15-56 h), high energy consumption, variable yields (from 15% to 85%), require great amounts of solvents, etc. This is why we decide to use for syntheses nonconventional methods, using microwave technology. The MW assisted reactions were carried out using a monomod reactor, using a constant irradiation power and varying the temperature. During a cycle the temperature rise up from the room temperature closely to the boiling point of solvents, then remains almost constant no matter the time was used. Initially we used for MW heating different reaction time (30, 15, 10, 5 min.), and different irradiation power of the magnetron (5, 10, 20, 25, 30%), but the best results were obtained at 5 min., using 25% from the full power of reactor (800 W). Table 1 lists the optimized conditions we employed, under MW irradiation as well as under classical heating.

As indicated in table 1, MW induced a remarkable acceleration for reactions, the reaction times decreasing dramatically, from hours to minutes (5 min.). Consequently, the consumed energy decreases considerably. In the most cases, under MW irradiation the yields are higher, in some cases substantially (with almost 75 percents). Moreover, the amount of used solvents is 5 times less (see experimental), these type of reactions being considered as environmentally friendly.

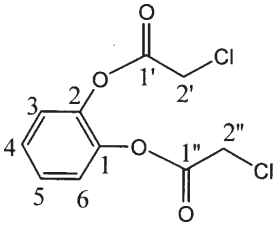
Both, under MW irradiation and classical heating, there is a difference of reactivity for benzene diols in the esterification reaction: 1,4-benzenediol is less reactive than benzene 1,2- and 1,3- benzenediols. This is proved by the



1. 1,2-OH
2. 1,3-OH
3. 1,4-OH

4. 1,2-O-; n=1 **7**. 1,3-O-; n=1 **10**. 1,4-O-; n=1
5. 1,2-O-; n=2 **8**. 1,3-O-; n=2 **11**. 1,4-O-; n=2
6. 1,2-O-; n=3 **9**. 1,3-O-; n=3 **12**. 1,4-O-; n=3

Scheme1. Reaction pathway of benzenediols with chloroacyl chloride



Scheme 2. NMR identification of H and C atoms

Compound	Microwaves		Classical	
	Reaction time, min.	Yield, %	Reaction time, hours	Yield, %
4 (1,2-OH)	5	96	17	75
5 (1,2-OH)	5	67	56	70
6 (1,2-OH)	5	95	28	85
7 (1,3-OH)	5	94	30	50
8 (1,3-OH)	5	60	53	80
9 (1,3-OH)	5	97	15	85
10 (1,4-OH)	5	90	55	15
11 (1,4-OH)	5	45	58	75
12 (1,4-OH)	5	85	45	55

Table 1
SYNTHESIS OF PHENYL BISESTER UNDER CLASSICAL HEATING AND MICROWAVE IRRADIATION IN LIQUUID PHASE

Table 2
INHIBITION ZONE (MEAN DIAMETER OF INHIBITION IN mm) AS A CRITERION OF ANTIBACTERIAL AND ANTIFUNGICAL ACTIVITIES OF SOME AROMATIC BISESTERS DESCRIBED IN THE TEXT

Strain→ Product and reference drug ↓	*S. aureus ATCC 25923*	*S. luteea ATCC 9341*	*B. cereus ATCC 14579*	*E. coli ATCC 25922*	*P. aerugino sa*	*Candida albicans*
Chloramphenicol, 30 mcg/disc	*30*	*40*	*28*	*25*	*19*	-
Nysatin, 100 mcg/disc	-	-	-	-	-	*29*
4	11	20	16	12	8	22
5	9	12	14	7	0	26
6	0	16	0	0	0	0
7	21	20	24	16	12	30
8	13	16	17	11	7	23
9	8	0	0	9	9	0

shorter reaction time (under classical heating) and by the higher yields (under MW) for benzene 1,2- and 1,3- diols.

There is also a certain difference of reactivity for chloroacyl chloride in the esterification reaction: under classical heating, the reaction time for 3-chloropropanoyl chloride it is almost double comparative with 2-chloroethanoyl chloride and 4-chlorobutanoyl chloride, which prove that the last two are more reactive. These difference of reactivity is confirmed under MW irradiation where we may notice that the yields are lower.

The structure of the new compounds was proven by elemental (C, H, N) and spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC). All the elemental and spectral data are in accordance with the proposed structure and are presented to the experimental part.

Biological activity

Having in view that some bisesters could have various biological activity [4-9] antimicrobial including, we decide to test the obtained compounds on different antimicrobial strains and, to establish structure - activity relationships in the aromatic bisesters series. Six bacterial strains were included in this study: *Staphylococcus aureus* ATCC 25923, *Sarcina lutea* ATCC 9341, *Bacillus cereus* ATCC 14579,

Escherichia coli ATCC 25922, *Pseudomonas aeruginosa* and fungus *Candida albicans*. The results are listed in table 2.

The comparative analysis of the data from table 2, leads to the conclusion that the aromatic esters derived from 1,3-benzenediol are the most active compounds against germs. There could be also noticed a certain influence of the side chain, esters with 2-chloro-acetoxy groups (**4** and **7**) being the most active.

Conclusion

A feasible study concerning syntheses, structure and biological activity of some new esters derived from 1,2-, 1,3- and 1,4- benzenediols is reported. Synthesis has been done both under classical heating and microwave irradiation. The microwave enhanced a remarkable rate of acceleration for esterification reaction (the reaction time decreasing dramatically), the reaction conditions are milder, the consumed energy decreases considerably and the amount of used solvents is reduced substantially. Consequently, the microwave assisted esterification reaction could be considered eco-friendly. A comparative study, microwave classical conditions (liquid solvents) was done. Antimicrobial activity of the newly obtained bisesters has been tested and, the tests prove that some esters compounds have a good activity against different microorganisms (germs and fungi). Correlations between structure and antimicrobial activity are reported.

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