Eco-friendly synthesis of 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives and antimicrobial evaluation of hydroxyls derivatives

Osmar C. Sanchez (PQ)[1*], Raúl R. Cairo (PG)[1], Edna D. Peralta (TC)[2], Angélica M. Lucchese (PQ)[2], Yamila V. Reyes (PQ)[1], Heiddy M. Alvarez (PQ)[2], Raynel Rojas (TC)[1], Yanier Núñez (PG)[3], Estael O. Rodriguez (PQ)[1]

1. Laboratorio de Síntesis Orgánica. Facultad de Química, Universidad de La Habana, Cuba. [2]Laboratório de Química de Produtos Naturais e Bioativos. Universidade Estadual de Feira de Santana, Bahia, Brasil. [3] Centro de Investigaciones y Desarrollo de Medicamentos, Ciudad Habana, Cuba. ***calderon@fq.uh.cu.***

Key words: Knoevenagel condensation, Meldrum´s acid, antimicrobial, synthesis in water.

Introduction

Arylidenmalonates had been thoroughly prepared starting from aromatic aldehydes and 1,3-dicarbonylic compounds by means of Knoevenagel condensation reaction using dry organic solvent [1]. In this work, we report the synthesis of several derivatives prepared through a heterogeneous reaction in aqua media, at room temperature, without catalyst.

Results

The synthesis of several arylidenmalonates derivatives was carried out through the Knoevenagel condensation reaction between the corresponding aromatic aldehydes and Meldrum´s acid. Three different homogeneous basic catalytic systems for three model reactions were tested, besides the free catalyzed reaction, all conducted in water with magnetic stirring at room temperature. It was found the catalysis process has a little influence in the overall reaction since all experiences proceed in a reasonably fast time (2-3 hours), with good yields (~80%). The products were collected by filtration, and washed with water or ethanol-water (50%) mixture, dried for two days and collected as amorphous solids. All products were characterized by NMR experiments, IR and UV spectroscopy. The corresponding melting points were also determined.

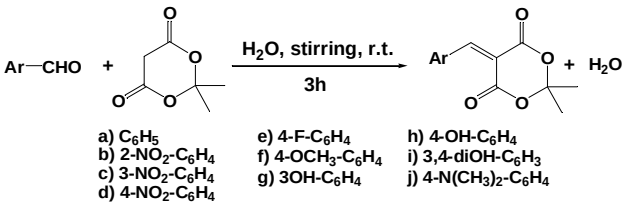

Figure 1. Synthetic scheme.

Hydroxyls derivatives (g, h and i) were selected to be submitted into antimicrobial testing against bacteria (*Escherichia coli CCMB261*, *Staphylococcus aureus CCBM 262*, *Pseudomonas aeruginosa CCMB 268*, according to CLSI 2003 and CLSI 2002 regulations respectively, using resazurine as developer. The results of Minimal Inhibitory Concentration (MIC) are presented in Table 1.

Tabela 1. Minimal Inhibitory Concentration (MIC)

	Minimal Inhibitory Concentration, mg.mL^{-1}		
Compound	***E. coli***	***S. aureus***	***P. aeruginosa***
G	0,69	0,38	0,69
H	Inactive	0,76	Inactive
I	0,69	0,76	0,69
Chloramphenicol	1,25	0,005	0,156

* Microorganism densities were adjusted to 1.5 X 10^8 CFU.mL^{-1} for bacteria. All compounds were dissolved in DMSO-H_2O (3:1) (V:V) mixture.

The 3,4-dydroxyl and the 3-hydroxyl derivatives were active against all evaluated bacteria, but the two gram negative bacteria were resistant to the 4-hydroxy compound.

Conclusions

Arylidenmalonates from Meldrum´s acid can be easily prepared at room temperature in water, without any catalyst, in about 3 h with good yields. Due to the use of water as solvent, as well as the absent of any thermal heating or catalyzer, the whole procedure can be regarded as an eco-friendly approach. These derivatives show antimicrobial activity. In general, 3-hydroxy and 3,4-dihydroxy derivatives were found active at lower concentration than the 4-OH derivative.

Acknowledgements

CAPES (CAPES/MES 61/09 project)

[1] Lipson V. V.; Gorobets N. Y, *Mol Divers*, **2009**, 13: 399 -419.