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Proceeding Paper

Kinetic Study of Acid-Catalyzed Knoevenagel Condensation Between 5-Methoxy-1-Tetralone and Glyoxylic Acid †

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Abstract: In this work we present, a kinetic study of the Knoevenagel condensation reaction between 5-methoxy-1-tetralone and glyoxylic acid, catalyzed by sulfuric acid, to produce (*E*)-2-(5-methoxy-1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)acetic acid. The reaction was carried out in a batch system at 400 rpm for 24 h at temperatures of 75, 80 and 85 °C. The yields obtained at these temperatures were 90.30, 93.75 and 94.16%, respectively. The reaction was monitored by TLC and HPLC. For the kinetic analysis, three mathematical methods were used: integral, differential and non-linear regression. The results showed an excellent fit of the experimental data to the pseudo-first-order kinetic model.

Keywords: kinetic study; acid catalyzed; Knoevenagel condensation; 1-tetralone

1. Introduction

1-Tetralones (3,4-dihydro-1*H*-naphthalene-1-ones), have been the subject of much interest in organic synthesis and natural products, as they possess a structure with the appropriate functional groups for building the skeletons of a wide range of products, making them a key starting material (Figure 1), particularly due to their potential as lead compounds in the pharmaceutical industry. Chemists worldwide have been interested in the isolation, synthesis and structural modification of 1-tetralone and its derivatives due to their importance in the synthesis of bioactive compounds such as steroids, prostaglandin analogues, dyes, heterocycles and pharmaceuticals and new drug candidates [1–7], as well as their use as fluorescent dyes or sensors [8].

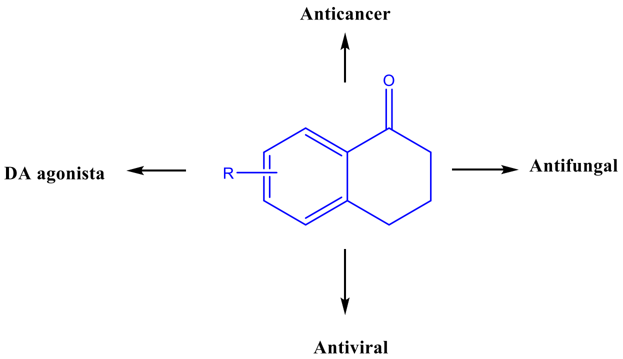

Figure 1. 1-tetralones moiety with various activities.

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In this study, we synthesized, characterized (*E*)-2-(5-methoxy-1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)acetic acid by a modification in acid medium of the Knoevenagel condensation reaction.

2. Materials and Methods

2.1. Materials and General Methods

All reagents were analytic grade and solvents previously purified by conventional methods. The reaction monitoring was carried out by thin layer chromatography (TLC) with silica plates. Products were purified by recrystallization using ethanol. Infrared spectra were obtained using a Perkin-Elmer Spectrum two FTIR spectrometer in a range of 500–4000 cm^{-1} and UV-Vis spectra were obtained using an Agilent Technologies Cary 60 UV-Vis spectrometer. Concentration data were obtained using an Agilent Technologies 1260 Series Infinity High Performance Liquid Chromatograph (RP-18 column, 150 × 4.6 mm). (1H, 13C) NMR spectra were recorded in CDCl3 on Bruker Avance-400 ((400.13 MHz (1H), 100.62 MHz (13C)) instruments.

2.2. Synthesis and Characterization

The compound (**1**) (400 mg, 2.27 mmol mmol) was added to diglyme (8 mL) and water (0.22 mL) and left in agitation, the glyoxylic acid (0.4 mL, 9.94 mmol) and a catalytic amount of sulfuric acid (0.03 mL) were added. The reaction mixture was heated to temperatures of 75 °C, 80 °C and 85 °C, with constant stirring at 400 rpm, for 24 h. For reaction monitoring, TLC and HPLC were performed at times ranging from the beginning at 0 h to the end at 24 h. The final product obtained (**2**) was recrystallized in ethanol and finally characterized by FTIR, 1H and 13C NMR, GC-MS. A yellow crystals, yield: 94%, Rf (dichloromethane, methanol and glacial acetic acid; 4.5:0.45:0.05) = 0.62. UV-vis (Ethanol) [λmax (nm)]: 260.1. IR (KBr) υmax (cm^{-1}): 3460. 61 (O-H), 1696.8 (C=O), 1673.6 (C=O α,β-insaturado). MS (EI) *m*/*z*: 214 $[M-H_2O]^+$, 186 $[M-CO]^+$, 171 $[M-CH_2]^+$. 1H-NMR (400 MHz, CDCl3, δ/ppm): 7.51 (d, 1Haromatic, J = 7.85 Hz), 7.32 (t, 1Haromatic, J = 7.95 Hz), 7.06 (d, 1Haromatic, J = 8.01 Hz), 6.86 (s, 1H, =CH-), 3.87 (s, 3H, O-CH3), 3.39 (t, 2H, -CH2), 2.99 (t, 2H, -CH2) and 13C-NMR (400 MHz, CDCl3, δ/ppm): 21.59, 26.82, 55.79, 115.01, 119.96, 122.15, 127.57, 133.34, 144.61, 152.10, 156.50, 171.61, 187.09.

3. Results and Discussion

Synthesis

The modified Knoevenagel condensation reaction in acidic medium generated the unsaturated acid of 1-tetralone (**3**) (Figure 2), obtaining results similar to those reported by Cheung et al. [9].

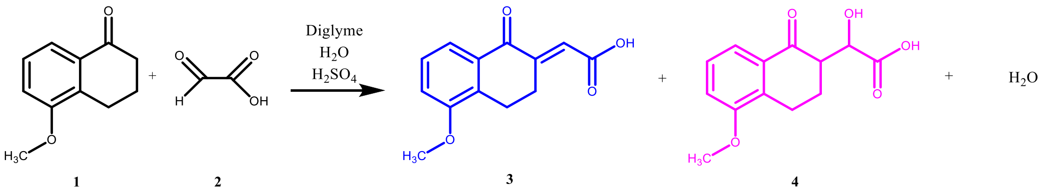
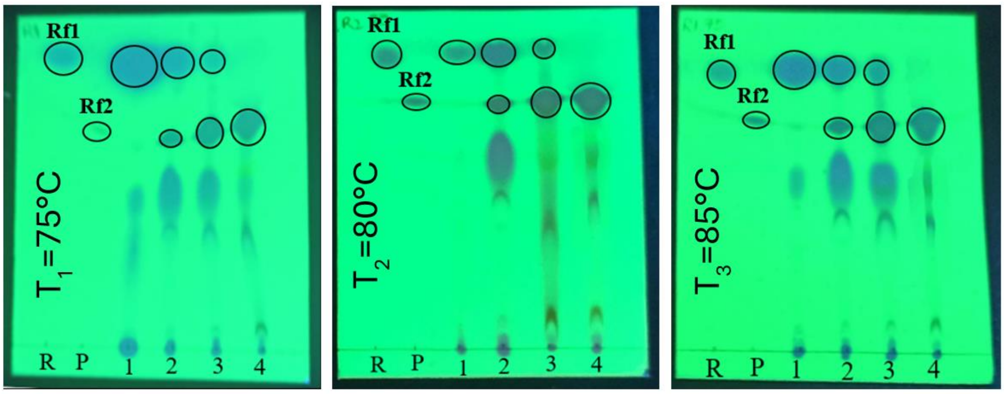


Figure 2. Scheme of the Reaction scheme Synthesis of (**3**).

In this study, the optimal conditions that allowed for the desired compound (**3**) to be obtained with a yield of 94.16% were: a reaction time of 24 h, stirring at 400 rpm, and a temperature of 85 °C. These conditions were determined by monitoring the reaction using thin-layer chromatography (TLC) (Figure 3), where the formation of a collateral product was observed, which was also analyzed by high-performance liquid chromatography (HPLC) (Figure 4).

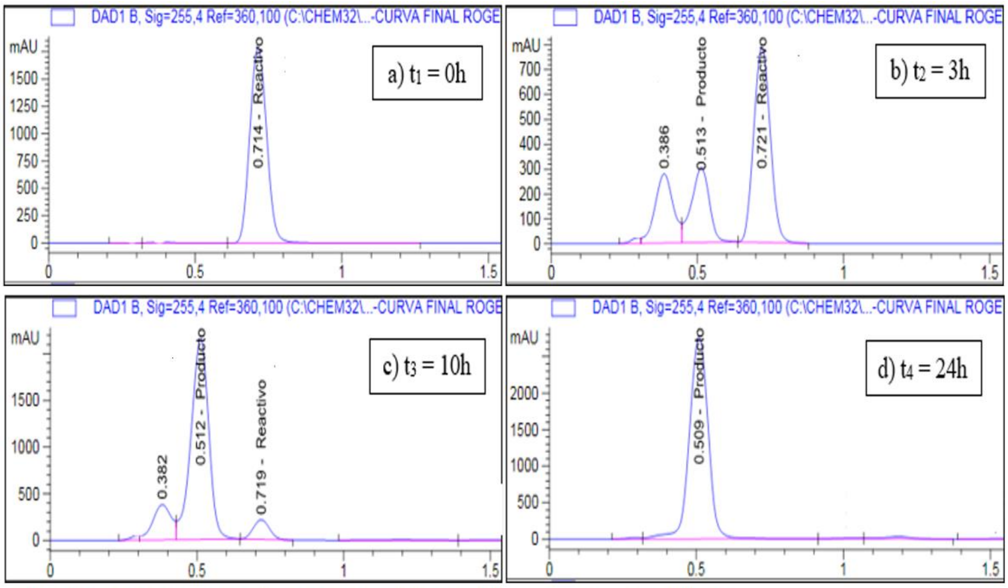


R: 5-methoxy-1-tetralone (1), P: reference, 1: time 1 (0h), 2: time 2 (3h), 3: time 3 (10h), 4: time 4 (24h)

Figure 3. Monitors the reaction using thin-layer chromatography (TLC).

According to Costantino et al. [10], during the reaction in basic medium (NaOH), the hydroxylated acid (**4**) is formed; however, its physical properties, characterization, and separation are not reported. In this study, it was possible to determine, by monitoring the reaction using HPLC, the time required for all starting material (**1**) and the intermediate (**4**) to be completely converted into the desired compound (**3**).

A variety of techniques were employed to ascertain the kinetic parameters, including the integral method, the differential method and non-linear regression. Of these, the non-linear regression method proved the most effective, demonstrating positive statistical metrics with a minimum deviation and acceptable coefficients between the experimental and calculated values.



Optimal conditions: reaction time of 24 hrs, stirring at 400 rpm, temperature of 85 °C

Figure 4. Monitors the reaction using High Performance Liquid Chromatograph (HPLC).

The study determined a kinetic behavior that approximates a pseudo first order in respect to 1. Additionally, the activation energy was calculated (Ea = 43.1014 kJ/mol), and thus a high sensitivity temperature dependence of the reaction for small changes was found. Finally, the yields obtained for the studied temperatures of 75, 80 and 85 °C were: 90.30, 93.75 and 94.16%, respectively (Table 1).

Table 1. Results of the kinetic parameters.

Parameters	1	2	3
Temperature, [°C]	75	80	85
Time, [h]	24	24	24
Yield, [%]	90.30	93.75	94.16
Reaction Order (α)	1.26	1.21	1.13
K, [(mL/mmol*min)$^{\alpha-1}$]	0.0129	0.0161	0.0196
Ea, [kJ/mol]		43.1014	
A [(mL/mmol*min)$^{\alpha-1}$]		8.4608×10^3	

4. Conclusions

In this work, the kinetic study of the Knoevenagel condensation reaction between 5-methoxy-1-tetralone and glyoxylic acid, catalyzed by sulfuric acid to produce (*E*)-2-(5-methoxy-1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)acetic acid was carried out. The ideal reaction parameters were 24 h time, 400 rpm and 85 °C for 94.16% yield, which were followed by TLC and HPLC. A pseudo first order reaction, kinetic constant (k = 0.0196 mL/(mmol*min)), pre-exponential factor (A = 8.4608×10^3 (mL/(mmol min)) and activation energy (Ea = 43.1014 kJ/mol) were determined for the rate law by nonlinear regression method, which provided the best model fit and statistical parameters. By FTIR, GC-MS and ^{1}H and ^{13}C NMR the product obtained was clearly identified and the purity.

Author Contributions: Conceptualization, M.E.H., E.V.C. and R.S.G.; methodology, R.S.G. and M.E.H.; investigation, E.V.C., M.E.H. and R.S.G.; writing—original draft preparation, E.V.C. and U.S.; writing—review and editing, E.V.C., R.S.G. and U.S.; supervision, EVC and M.E.H. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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