

Kinetic Study of the Pyridine-Catalyzed Selenolactonization of 4-Pentenoic Acid

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Received: 1 November 2019 / Accepted: 15 January 2020 © Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

The kinetics and mechanism of the pyridine-catalyzed cyclofunctionalization of 4-pentenoic acid by means of PhSeX (X = CI, Br) have been investigated spectrophotometrically, under *pseudo*-first order reaction conditions. The influence of the reaction temperature, the type of cyclization reagent and used catalyst on the reaction rate and mechanism was examined. The obtained data have showed that rate constants go on increasing as the temperatures go up and with use of PhSeCl as reagent. Also, the reaction rate is directly depended on the type of the catalyst used—stronger bases with higher tendency for hydrogen bond formation (DN) are promoting reaction in more efficient way.

Graphic Abstract



Keywords Kinetics · Lactone · Pyridine · Selenium

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10562-020-03107-0) contains supplementary material, which is available to authorized users.

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1 Introduction

Gama lactones present a unique class of organic compounds due to their presence as key structural units in numerous biologically active molecules, as well as due to their potential to serve as building blocks for the total synthesis of natural products [1]. The gamma-lactone motif has been present in more than one third of natural products. Moreover, its presence in the core of the fungal, marine or bacterial sourced-biomolecules is distinctive for the wide range of expressed biological activities [2–4]. Therefore, modern science is setting an imperative in front of organic chemists for development of new and improvement of existing methodologies for the selective synthesis of gamma lactone

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Scheme 1 Mechanistic survey of the selenolactonization of 4-pentenoic acid. The effect of the pyridine as catalyst in selonalactonization

molecules. Under these circumstances, a lot of effective methods for the lactone ring have arisen in literature [5-10]. One of the commonly utilized approaches is the cyclofunctionalization of the alkenoic acids [11–15]. Depending on the substrate substitution pattern, type of reagent used or presence of external catalyst, a great structural variety of the target lactone molecules can be achieved. The application of the organoselenium-based molecules as reagents for cyclofunctionalization of alkenoic acids has many advantages which are reflected in high regioselectivity, acceptable yields of lactone products and easy manipulation with the organoselenium part in side chain of lactone ring [16–18]. From these reasons, organoselenium-induced selenolactonizations have been utilized in total synthesis of the natural products containing lactone-ring in structure. Despite the synthetic utility of the organoselenium-based lactonization of unsaturated acids, the literature survey still suffers from the moderate number of mechanistic reports for these reactions. The examination of the reaction transformations at the mechanistic level is important due to the possibility for the process optimization and improvement in the term of yields, selectivity and reaction rates.

Our group has been involved in long-term kinetic studies of the related cyclofunctionalization of unsaturated alcohols by organoselenium reagents in the presence of different Lewis bases and acids as catalysts [19–27]. In an extension of our previous studies and on the base of our earlier findings, herein we are presenting results of mechanistic and kinetic study of the cyclofunctionalization of the 4-pentenoic acid by PhSeCl and PhSeBr, in the presence of the pyridine as catalysts.

2 Results and Discussion

The reaction between 4-pentenoic acid 1 and PhSeX (X = Cl, Br) is resulting in formation of basic example of seleno-functionalized gamma-lactone 2 (Scheme 1). The typical reaction mechanism of these reactions involves: a) electrophilic addition of the electrophilic reagent PhSeX (X = Cl, Br) on double bond of 4-pentenoic acid 1, which has formation of positively charged selenonium cation I as intermediate for result. This step activates C-C bond for the subsequent nucleophilic attack of the oxygen from COOH group and formation of protonated salt II. Finally, fast removal of the proton attached to the oxygen atom releases the final lactone product 2. Due to the presence of halide anion from PhSeX reagent (Cl or Br), the reaction can also follow second pathway and formation of addition product 3 can occur. In order to prevent side reaction, as well as to increase nucleophilicity of the oxygen in carboxylic group, the presence of catalyst is necessary. It is well known that the bases (such as pyridine, triethylamine, NaHCO₃) in this type of chemical transformations could prevent prolonged reaction time and excess of reagent used. This feature can be attributed to the different ways in which base could act in selenolactonization reaction: bases have ability to abstract hydrogen from the carboxylic group and, on that way, to increase nucleophilic power of oxygen from COOH group for the attack on the activated C–C bond in seleniranium cation (Scheme 1). The newest researches [28, 29] have indicated that Lewis bases increase electrophilicity of the weak electrophilic PhSeX reagents, by the coordination of Lewis base donor to PhSeX electrophile and net polarization of the obtained Lewis acid-base adduct. The result of this process is formation of the highly electrophilic selenonium cation,



Fig. 1 Kinetic traces for the reaction between PhSeCl and 4-pentenoic acid, in the presence of pyridine, at 308 K (λ =250 nm)

which can be captured by the COOH group to afford desired lactone (Scheme 1).

For more detailed insight into kinetic and mechanistic aspects of the pyridine-mediated phenylselenolactonization of the 4-pentenoic acid, we performed kinetic investigation using conventional UV–Vis method [30]. The study has involved the investigation of the influence of the temperature variation, as well as variation of the cyclization reagent (PhSeCl or PhSeBr) on the reaction rates. In addition, activation parameters of the reaction—entropy and enthalpy of activation have been determined.

The reactions were processed under *pseudo*-first order conditions, at three different temperatures (288, 298 and 308 K), in THF as solvent. The temperature of all reacting solutions was controlled at ± 0.1 °C. Rate constants have been obtained by spectrophotometrically monitoring of the decay of the absorbance of the 4-pentenoic acid at suitable wavelength (Fig. 1). Kinetic runs were performed by adding adequate amounts of reagent and catalyst solution to a 4-pentenoic acid solution contained in spectrometer cuvettes that has been allowed to reach temperature equilibrium with the spectrometer cell compartment. The data obtained suited to the *pseudo*-first order rate law well and



Fig. 2 Observed rate constants for the *pseudo*-first order reaction as a function of 4-pentenoic acid concentration at different temperatures

 Table 1
 Rate constants and activation parameters for the phenylselenolactonization of 4-pentenoic acid with PhSeCl and PhSeBr in the presence of pyridine

T (K)	PhSeCl+Pyridine				PhSeBr+Pyridine			
	$\overline{k_2 (\mathrm{M}^{-1} \mathrm{s}^{-1})}$	$k_1 ({ m s}^{-1})$	$\Delta H^{\#} (kJM^{-1})$	$\Delta S^{\#} \left(\mathbf{J} \mathbf{K}^{-1} \mathbf{M}^{-1} \right)$	$\overline{k_2 (\mathrm{M}^{-1}\mathrm{s}^{-1})}$	$k_1 (s^{-1})$	$\Delta H^{\#} (\mathrm{kJM^{-1}})$	$\Delta S^{\#} \left(\mathbf{J} \mathbf{K}^{-1} \mathbf{M}^{-1} \right)$
288	0.42 ± 0.03	1	16±2	-210 ± 7	0.29 ± 0.01	/	14 <u>+</u> 1	-223 ± 2
298	0.52 ± 0.06	/			0.36 ± 0.02	/		
308	0.70 ± 0.02	/			0.45 ± 0.03	/		

Table 2 Comparison between rate constants for the reaction of 4-pentenoic acid selenocyclofuntionalization by means of PhSeX (X = Cl, Br), in the presence of pyridine and trimethylamine as catalysts

Т	PhSeCl+Pyridine	PhSeCl+ $Et_3N[25]$	PhSeBr + Pyridine	PhSeBr + $Et_3N[25]$
308	0.70 ± 0.02	1.36 ± 0.06	0.45 ± 0.03	0.84 ± 0.02
298	0.52 ± 0.06	0.92 ± 0.04	0.36 ± 0.02	0.6 ± 0.03
288	0.42 ± 0.03	0.64 ± 0.02	0.29 ± 0.01	0.44 ± 0.02

observed *pseudo*-first order constants are determined by least squares fitting of an exponential function.

Observed *pseudo*-first order constants, k_{obsd} , are described by the following equation, where the values of the k_2 constants correspond to the rate of the forward reaction—cyclofunctionalization, while the k_1 constants describe the effect of the side reaction (addition of the electrophile organoselenium reagent to the double bond, formation of the product 3 in Scheme 1). k_2 values are calculated from the slopes of the plots k_{obsd} vs. 4-pentenoic acid concentration, while k_1 values have been derived from the intercepts in the same plots (Fig. 2, Table 1).

$$k_{\text{obsd}} = k_1 + k_2 [4 - \text{pentenoic acid}]$$

Kinetic parameters derived from this equation (Table 1) have demonstrated dependence of the reaction rate on the reaction temperature, as well as dependence on electrophilic source used. In all investigated reactions, reaction rates increase with an increase in reaction temperature. In addition, all tested cases have showed increasing tendency for rate constants for PhSeCl as reagent, in comparison to the PhSeBr where rate of reactions was lower. The effect of the side reaction, which is described by the k_1 constants, is negligible in comparison to the forward reaction and therefore, these values are not showed in Table 1. Comparison of the rate constants obtained in this study with analogues values for the reactions where triethylamine was used as catalyst [26] (Table 2), has revealed that triethylamine has stronger potential for rate increasing than pyridine. Although these two catalysts are acting in quite similar way in synthetic investigation (the presence of both catalysts are increasing yields of the lactone up to 100%), kinetic investigation has

demonstrated the rate constants almost two times higher in the case of triethylamine. This can be explained by the fact that triethylamine is stronger base than pyridine (pKa (Et₃N) = 10.75; pKa (Py) = 5.25), and also has higher donor number (DN (Et₃N) = 61; DN (Py) = 33.1). These two features are responsible for the activation of the electrophilic PhSeX reagent toward formation of the selenonium cation, or for the activation of the COOH group for the nuclephilic attack on the selenonium cation.

By the fitting values for rate constants to the Eyring equation, the activation parameters have been obtained (Fig. 3). Their values are presented in Table 1. Variation in the reagent type and catalyst used is not influencing the reaction mechanism, and the negative values for entropy of activation values are supporting S_N^2 mechanism of the OH nucleophilic attack on the selenonium cation.

$$\ln\left(\frac{k_2}{T}\right) = -\frac{\Delta H^{\neq}}{RT} + \left[\ln\left(\frac{k_2}{T}\right) + \frac{\Delta S^{\neq}}{R}\right]$$



Fig. 3 Eyring equation plot for the reaction between 4-pentenoic acid and PhSeBr in the presence of pyridine

3 Conclusion

The kinetics and the mechanism of the pyridine-catalyzed selenolactonization of the 4-pentenoic acid have been reviewed. The achieved results in the kinetic study have revealed that reaction rates depend on the reaction temperature (increasing rate constants with an increase in temperature), as well as on the type of the organoselenium reagent used (PhSeCl is more reactive than PhSeBr). In addition, this study has confirmed tight relation between catalyst basicity and ability for formation of hydrogen bond and values of rate constants. Stronger bases with better ability for proton abstraction (DN) are promoting reaction in more efficient way. The variation in reagent and catalyst used is not influencing change in reaction mechanism.

4 Experimental Section

4.1 General Information

Commercial reagents and solvent were used without further purification.

4.2 Kinetic Measurements

UV–VIS Perkin Elmer Lambda 35 spectrophotometer equipped with a thermostated cell was used for the kinetic measurements.

The conventional kinetic method was used for the determination of the rate constants [30]. The temperature of reaction solutions was maintained throughout all probes to ± 0.1 °C. Reactions were followed at 288, 298 and 308 K. The calculated amounts of the reactants were measured and dissolved in THF, in order to prepare reaction solutions. Firstly, in a quartz cuvette a certain volume of acid solution was added, followed by the addition of the pyridine solution and the reaction were initiated by adding phenylselenyl halide. The concentration of phenylselenyl halide was maintained constant $(1 \times 10^{-4} \text{ M})$ during all experiments, while the concentration of acid was changing from 5×10^{-3} M, 4.5×10^{-3} M, 4×10^{-3} M, 3.5×10^{-3} to 3×10^{-3} M. The pyridine concentration was equimolar to phenylselenyl halide concentration. The reactions were elucidated by following the dependence of the absorbance on reaction time at suitable wavelength. For the determination of *pseudo*-first rate constants, k_{obsd} , following equation was used.

$$\mathbf{A}_{t} = \mathbf{A}_{0} + (\mathbf{A}_{0} - \mathbf{A}_{\infty}) \exp(-k_{\text{obsd}}t)$$

All kinetic runs were fitted as single exponential function. The obtained *pseudo*-first order rate constants present average value from two to five independent kinetic runs using Microsoft Excel and Origin 6.1.

Acknowledgements This work was funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant: 172011). This research is part of the thematic multidisciplinary network SeS Redox and Catalysis.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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