

# A KINETIC STUDY OF THE REACTION BETWEEN 2-p-METHOXYPHENYL-4-PHENYL-2-OXAZOLIN-5-ONE AND 2,2,6,6-TETRAMETHYL-1-PIPERIDINYL-N-OXIDE

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## ABSTRACT

The reaction between 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one and 2,2,6,6-tetramethyl-1-piperidiny-N-oxide (TEMPO) in benzene as the solvent generates quantitatively 4,4'-bis-[2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one]. Studies performed by means of EPR spectroscopy and kinetic experiments carried out using UV-VIS spectrophotometry have shown that the reaction occurs via a captodative radical intermediate. Kinetic experiments lead to a rate constant equal to  $1.38 \times 10^{-2} \text{ s}^{-1}$  and a reaction rate law which is first order in oxazolinone and independent of TEMPO concentration. These results are explained in terms of a reaction mechanism with a rate-limiting step involving the formation of a mesoionic tautomer of oxazolinone. Hydrogen abstraction from the mesoion by TEMPO gives captodative radicals that generate the observed product through a fast recombination reaction.

**KEY WORDS:** 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one, TEMPO, 4,4'-bis-[2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one], 4,4'-dehydrodimers, captodative radicals.

## RESUMEN

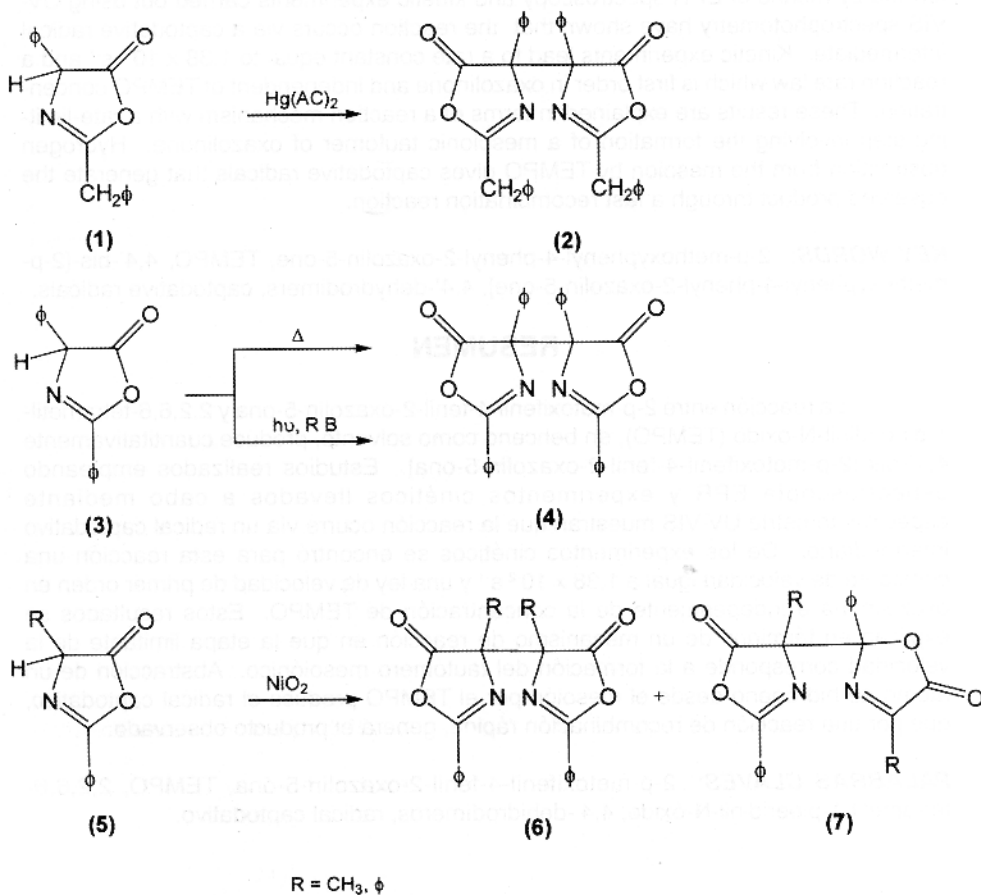
La reacción entre 2-p-metoxifenil-4-fenil-2-oxazolin-5-ona y 2,2,6,6-tetrametil-1-piperidinil-N-óxido (TEMPO), en benceno como solvente, produce cuantitativamente 4,4'-bis-[2-p-metoxifenil-4-fenil-2-oxazolin-5-ona]. Estudios realizados empleando espectroscopía EPR y experimentos cinéticos llevados a cabo mediante espectrofotometría UV-VIS muestran que la reacción ocurre vía un radical captodativo intermediario. De los experimentos cinéticos se encontró para esta reacción una constante de velocidad igual a  $1,38 \times 10^{-2} \text{ s}^{-1}$  y una ley de velocidad de primer orden en oxazolinona e independiente de la concentración de TEMPO. Estos resultados se explican en términos de un mecanismo de reacción en que la etapa limitante de la velocidad corresponde a la formación del tautómero mesoiónico. Abstracción de un átomo de hidrógeno desde el mesoión por el TEMPO produce el radical captodativo, que por una reacción de recombinación rápida, genera el producto observado.

**PALABRAS CLAVES:** 2-p-metoxifenil-4-fenil-2-oxazolin-5-ona, TEMPO, 2,2,6,6-tetrametil-1-piperidinil-N-óxido, 4,4'-dehidrodímeros, radical captodativo.

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### INTRODUCTION

2,4-Disubstituted  $\Delta^2$ -oxazolin-5-ones yields 4,4'-dehydrodimers when dissolved in polar solvents such as dimethylsulfoxide or dimethylformamide, in the presence of oxygen<sup>1-3</sup>. This process has been explained in terms of the reaction between the mesoionic form of oxazolinone and molecular oxygen to give a captodative radical that reacts mainly via dimerization<sup>4</sup>. Captodative free radicals have been proposed as intermediate in several reactions involving  $\Delta^2$ -oxazolin-5-ones. Examples of these reactions are included in Scheme 1: the reaction of 2-phenyl-4-benzyl-2-oxazolin-5-one (1) with mercuric acetate to yield the corresponding 4,4'-dehydrodimer<sup>1</sup> (2); the production of 4,4'-bis-[2,4-diphenyl-2-oxazolin-5-one] (4) by heating of 2,4-diphenyl-2-oxazolin-5-one (3) under reduced pressure<sup>3</sup>; the sensitized photooxidation of 2,4-diphenyl-2-oxazolin-5-one (3) in the presence of Rose Bengal to give the 4,4'-dehydrodimer<sup>5</sup> (4); and the reactions of  $\Delta^2$ -oxazolin-5-ones 2,4-diaryl or 2-aryl-4-methyl substituted oxazolinones (5) with nickel peroxide in benzene to yield 4,4' (6) and/or 4,2'-dehydrodimers (7)<sup>6</sup>. In these works the presence of a free radical located at C-4 of the oxazolinone ring, which is stabilized by the carbonyl group at C-5 and the imino bond between positions 2 and 3 at the other side in the ring system, has been proposed as the intermediate that yields the observed products. However, it has not been published spectroscopic studies and/or kinetic experiments to demonstrate the validity of these propositions and the participation of captodative radicals in these reactions. The presence of these intermediates has been suggested only considering the analysis of product distribution.



SCHEME 1

In this work, we study the reaction between 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one (**8**) and 2,2,6,6-tetramethyl-1-piperidiny-N-oxide (TEMPO) (**9**) that generates quantitatively the dimeric product 4,4'-bis[2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one] (**10**). Spectroscopic and kinetic evidences to support a free radical intermediate preceding the 4,4'-dehydrodimer are also provided.

## EXPERIMENTAL

The following compounds: 2,2,6,6-tetramethyl-1-piperidiny-N-oxide, D,L- $\alpha$ -phenylglycine, p-methoxybenzoylchloride (Aldrich Chemical Co.) were used without previous purification. Acetic anhydride (Aldrich Chemical Co.) was distilled immediately before use. All solvents used (Merck) were spectroscopic or HPLC grade.

NMR spectra were performed in a Bruker DRX-300 spectrometer. Chemical shifts were expressed in ppm, using tetramethylsilane, TMS, as an internal standard.

EPR spectra were obtained in a Bruker ECS 106 spectrometer operated in the X band.

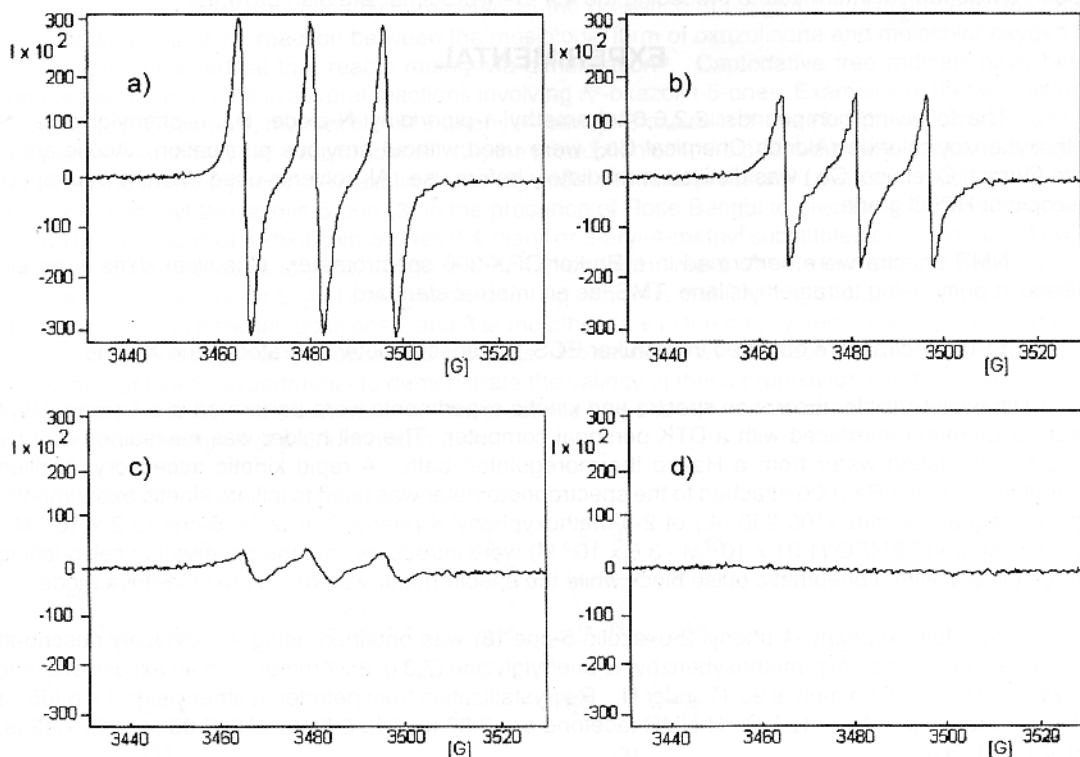
Ultraviolet-Visible absorption spectra and kinetic experiments were performed in a Unicam UV-4 spectrophotometer interfaced with a DTK personal computer. The cell holder was maintained at  $22 \pm 0.5^\circ\text{C}$  by circulating water from a Haake thermoregulated bath. A rapid kinetic accessory, Applied Photophysics model RX1000 attached to the spectrophotometer was used to initiate kinetic experiments. Typically, equal volumes (100-250  $\mu\text{L}$ ) of 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one ( $9.2 \times 10^{-4} \text{ M}$  -  $3.6 \times 10^{-3} \text{ M}$ ) and TEMPO ( $1.91 \times 10^{-2} \text{ M}$  -  $3.6 \times 10^{-2} \text{ M}$ ) were introduced into the observation cell pushing syringe pistons with a pneumatic pulse block while the spectrometer was run in the time drive mode.

2-p-Methoxyphenyl-4-phenyl-2-oxazolin-5-one (**8**) was obtained using a previously described procedure<sup>7</sup>, by reaction of p-methoxybenzoyl- $\alpha$ -phenylglycine (7.3 g, 25.7 mmol) with an excess of acetic anhydride (15.7 g, 154 mmol) at  $90^\circ\text{C}$  under  $\text{N}_2$ . Recrystallization from petroleum ether yields 4.4 g (65%) of the product, m.p. =  $123 - 124^\circ\text{C}$ ,  $^1\text{H-NMR}$  (acetone- $d_6$ ): 3.87 (s, 3H); 5.61 (s, 1H); 7.05 (d, 2H); 7.42 (s, 5H); 7.98 (d, 2H).

4,4'-bis-[2-p-Methoxyphenyl-4-phenyl-2-oxazolin-5-one] (**10**) was synthesized by reaction of 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one (0.1 g, 0.37 mmol) with a slight excess of 2,2,6,6-tetramethyl-1-piperidiny-N-oxide (0.063 g, 0.4 mmol) in benzene at ambient temperature. Recrystallization from benzene-petroleum ether yields 0.097 g (97%) of the dimer, m.p. =  $194.5-195^\circ\text{C}$ ,  $^1\text{H-NMR}$  (acetone- $d_6$ ): 3.87 (s, 6H); 6.8-8.1 (m, 18H).

## RESULTS AND DISCUSSION

The reaction of 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one with a small excess of TEMPO in benzene at ambient temperature produces 4,4'-bis-[2-methoxyphenyl-4-phenyl-2-oxazolin-5-one] in quantitative yield. The formation of dehydrodimer is very clean and no secondary products are produced as in the oxidative dimerization of the same oxazolinone with nickel peroxide<sup>6</sup>. The radical character of the reaction can be easily established from simple EPR experiments. Figure 1 a) shows the EPR spectrum of a solution  $9.5 \times 10^{-3} \text{ M}$  of TEMPO in benzene, which is comparable to the previously described spectrum for the same molecule<sup>8,9</sup>. Figure 1 b) shows the EPR spectrum of the sample run immediately after adding  $1 \times 10^{-2} \text{ M}$  of 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one and Figures 1c) and 1d) show the EPR spectra of the sample obtained 3 min and 10 min following oxazolinone addition, respectively. These experiments show a fast TEMPO consumption once a stoichiometric quantity of oxazolinone is added to the measuring cell and can be interpreted in terms of the reaction of TEMPO with the heterocyclic compound to give a free radical probably centered on a carbon atom of the heterocyclic ring. In addition, no other EPR signal was detected in the sample throughout the course of the reaction or after total TEMPO consumption, a result indicative of a fast recombination of oxazolinone centered radical to give the dimeric product observed. Although free radicals have been claimed to explain product distribution in reactions of substituted oxazolinones with several substrates, the reaction mechanism is not well understood. In the



**FIG. 1.** a) EPR spectrum of TEMPO  $9.5 \times 10^{-3}$  M in benzene; b) EPR spectrum of the same sample obtained immediately after adding  $1 \times 10^{-2}$  M of 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one; 1c) and 1d) EPR spectra of the same sample obtained 3 min and 10 min, respectively, following oxazolinone addition.

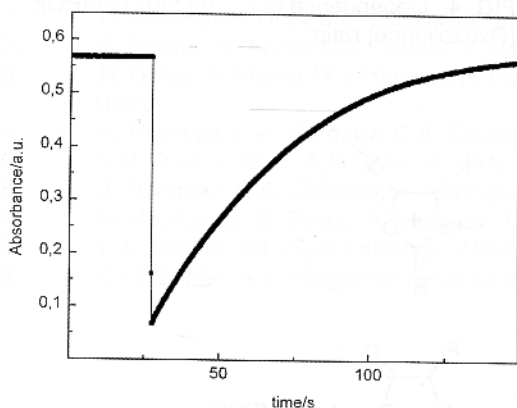
reactions of  $\Delta^2$ -oxazolin-5-ones 2,4-disubstituted with nickel peroxide in benzene<sup>6</sup>, it has been proposed that the hydroxyl radical associated to excess hydrogen and oxygen in the peroxide directly abstracts a hydrogen atom from the oxazolinone to produce a captodative radical at C-4. It has also been suggested that secondary products such as 2,4-dehydrodimer and amide derivatives are generated from a radical at C-2 in equilibrium with the radical initially formed. Otherwise, the oxidative dimerization of  $\Delta^2$ -oxazolin-5-ones 2,4-disubstituted by molecular oxygen in polar solvents such as dimethylsulfoxide has been rationalized in terms of electron transfer from the mesoionic form of oxazolinone at the oxygen molecule to give superoxide radical anion and a radical cation of oxazolinone<sup>1-3</sup>). Further reaction between these intermediates produces hydroperoxide radical and a captodative radical stabilized at C-4 of the heterocycle, which reacts mainly by dimerization. In order to determine if interaction of TEMPO with 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one occurs via mesoionic or ketonic tautomer, we studied the kinetics of this reaction under several experimental conditions.

Benzene was selected to carry out our kinetic experiments because no dimer formation by oxidative dimerization was detected in this solvent after 24 h of stirring at ambient temperature. Also, an excess of TEMPO from 5 to 63 times the oxazolinone concentration, was employed. In these conditions, the reaction proceeds to completion in about 100 s, a reason why it was necessary to initiate the reaction by means of a rapid kinetic accessory attached to the measuring cell.

It was also indispensable to determine the appropriate wavelength to follow the reaction spectrophotometrically since both compounds, the oxazolinone and the dimeric product, absorb in same spectral region and the spectra of both compounds overlap appreciably. However, above 310 nm the molar absorptivity coefficient of the dimer is significantly larger than the molar absorptivity of the oxazolinone. As a result, a wavelength of 340 nm was selected to monitor the reaction kinetics observing the rate of dimer apparition, since at this wavelength the contribution of the monomeric compound to absorbance can be considered irrelevant.

Figure 2 shows the increase of dimer concentration at 340 nm, observed in a typical kinetic experiment performed by mixing equal volumes of 0.0191 M TEMPO and 0.00108 M oxazolinone in benzene. If data are fitted according to equation 1:

$$\ln \frac{A_{\infty} - A_0}{A_{\infty} - A_t} = k t \quad (1)$$



**FIG. 2.** Increase of dehydrodimer concentration at 340 nm, observed in a kinetic experiment performed by fast mixing of equal volumes of 0.0191 M TEMPO and 0.00108 M oxazolinone in benzene.

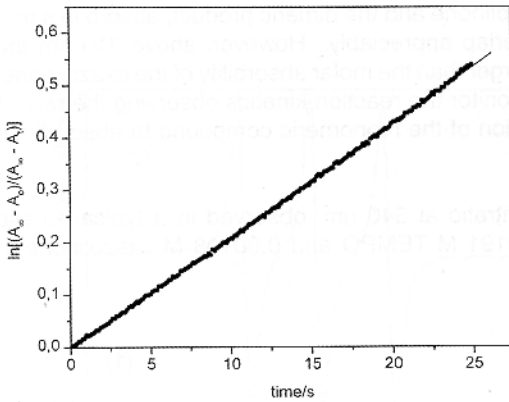
where  $A_{\infty}$ ,  $A_0$  and  $A_t$  are the absorbances at time  $\infty$ , time 0 and time  $t$  measured at 340 nm, a linear plot, shown in Figure 3, is obtained. This result is compatible with a pseudo first order kinetics. Then, from the quotient between the slope of the pseudo first order plots and the corresponding TEMPO concentration, values of the experimental rate constant,  $k_{\text{exp}}$ , for the reaction between the oxazolinone and TEMPO can be determined. Values of  $k_{\text{exp}}$  calculated by this method were independent of the ratio between oxazolinone and TEMPO concentration, as depicted in Figure 4, indicating that the reaction is zero order in TEMPO. From the plot in Figure 4, a mean value of  $k_{\text{exp}}$  equal to  $1.38 \times 10^{-2} \text{ s}^{-1}$  is obtained. According to these results, the kinetics for the reaction between 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one and 2,2,6,6-tetramethyl-1-piperidiny-N-oxide can be described by equation 2:

$$v = k_{\text{exp}} [\text{OXA}] \quad (2)$$

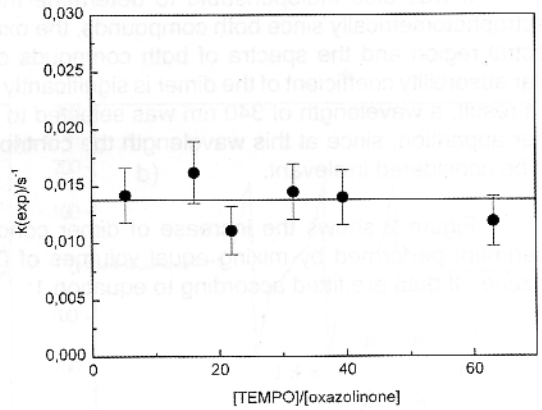
The kinetic law can be explained by considering the mechanism in Scheme 2.

Scheme 2 shows that in a first step equilibrium is established between keto and mesoionic tautomers of oxazolinone. In a second step, hydrogen abstraction from the mesoionic form of the heterocycle by TEMPO occurs. Finally, recombination of captodative radicals centered at position 4 of the heterocyclic ring, generated by rearrangement of primary radicals produced in step 2, gives the observed dimeric product.

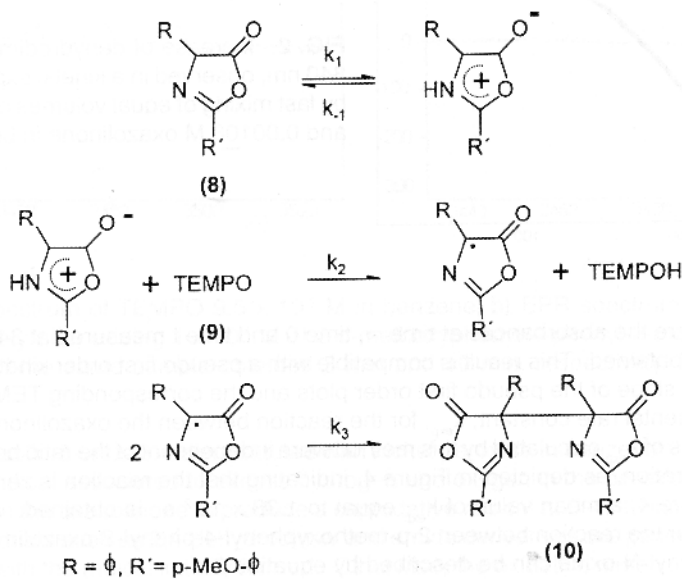
From the mechanism represented in scheme 2, the rate of product formation can be obtained as:



**FIG. 3.** Plot of  $\ln[(A_{\infty} - A_0)/(A_{\infty} - A_t)]$  vs time, for a kinetic experiment performed by fast mixing of equal volumes of 0.0191 M TEMPO and 0.00108 M oxazolinone in benzene.



**FIG. 4.** Dependence of  $k_{\text{exp}}$  on the  $[\text{TEMPO}]/[\text{Oxazolinone}]$  ratio.



**SCHEME 2**

$$v = \frac{k_1 k_2 [\text{OXA}][\text{TEMPO}]}{k_{-1} + k_2 [\text{TEMPO}]} \quad (3)$$

if equilibrium between the keto and mesoionic forms is reached slowly and hydrogen abstraction from the mesoionic tautomer by TEMPO occurs quickly, the condition  $k_2 [\text{TEMPO}] \gg k_{-1}$  applies and the reaction rate law takes the form:

$$v = k_1 [\text{OXA}] \quad (4)$$

This kinetic equation equals the one obtained experimentally if  $k_{\text{exp}} = k_1$ . From these results it can be pointed that the rate limiting step in the mechanism corresponds to the formation of the mesoionic tautomer of oxazolinone.

In conclusion, the reaction of 2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one with 2,2,6,6-tetramethyl-1-piperidiny-N-oxide yields the dehydrodimer of oxazolinone quantitatively. The reaction mechanism involves hydrogen abstraction from the mesoionic tautomer of oxazolinone to give a captodative radical centered at C 4 in the heterocyclic ring, a process that corresponds to the rate-limiting step. Product formation occurs by fast recombination of the captodative radicals.

### ACKNOWLEDGEMENTS

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