

# Synthesis of 4-Arylallylidene-pyrazolone Derivatives †

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**Abstract:** Pyrazoles and their derivatives have attracted particular attention because they have a wide variety of biological activities, and recently, we found that 4,4'-(arylmethylene)-bis-(1-phenyl-3-methyl-1*H*-pyrazole-5-ols) have good leishmanicidal activity against promastigotes of *Leishmania mexicana*. 4-Arylidenepyrazolone derivatives also have antiparasitic activity and are intermediates in the synthesis of these bispyrazoles that are formed by the equimolar reaction of 3-methyl-1-phenyl-2-pyrazoline-5-one with aromatic aldehydes. In order to obtain new compounds with potential leishmanicidal activity, we attempted to synthesize several 4-arylallylidene-pyrazolone derivatives through the reaction of pyrazol-3-one with different cinnamaldehydes. We report here the study of the synthesis of some 4-arylallylidene-pyrazolone derivatives from the reaction between 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one and 4-nitrocinnamaldehyde. We found that *L*-proline and FeCl<sub>3</sub> were the best catalysts, and we also observed a solvent effect in the reaction. Our preliminary results indicate that aprotic solvents favor the formation of the *ZZ* isomer instead of the *ZE* isomer.

**Keywords:** pyrazoles; 4-arylallylidene-pyrazolones; cinnamaldehydes; valence isomerization



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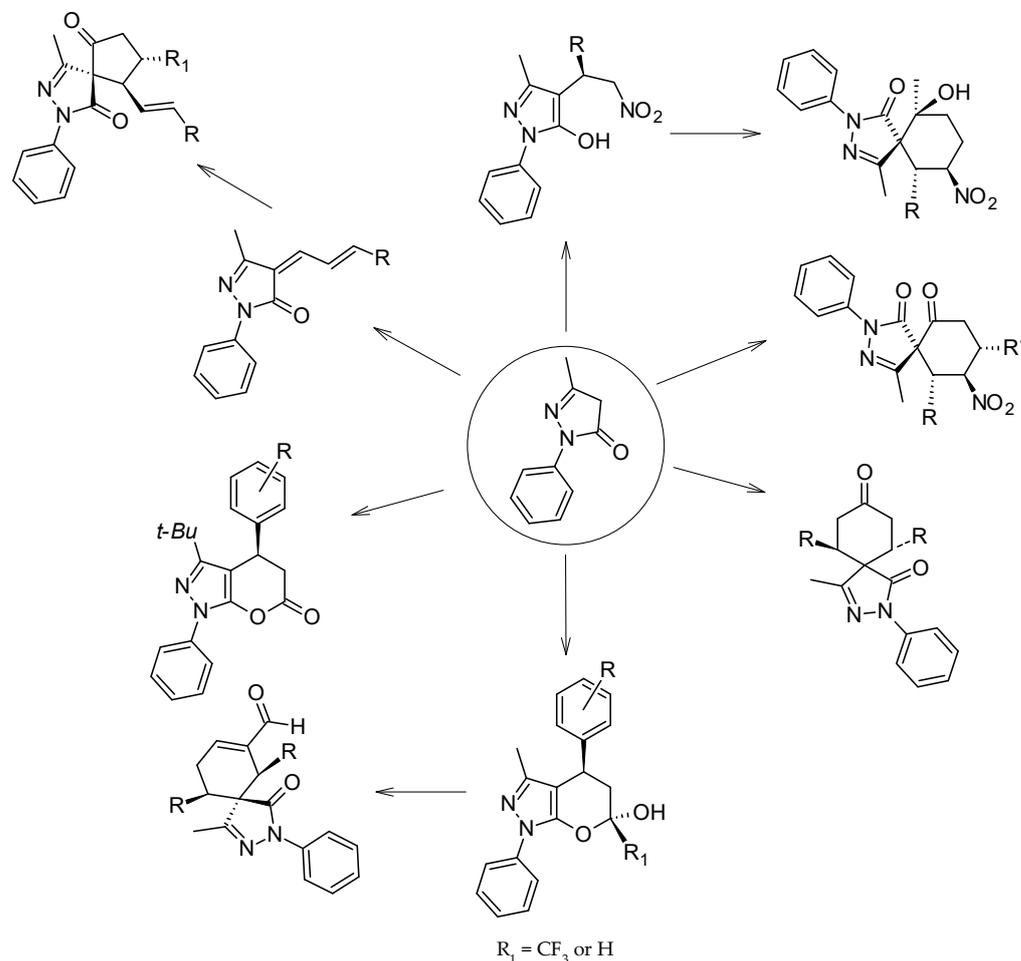
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## 1. Introduction

In heterocyclic chemistry, pyrazolones correspond to a type of important molecules with a wide range of reported biological activities. Currently, several drugs on the market possess the pyrazolone ring as a key structure, and its presence confers a wide range of properties such as anti-inflammatory, antiviral, antibacterial, antifungal, and antiparasitic activities, among others [1]. Derivatives of 2,4-dihydro-3*H*-pyrazol-3-one include edaravone and 4,4'-(arylmethylene)bis(1-phenyl-3-methyl-1*H*-pyrazol-5-ol). Edaravone, (3-methyl-1-phenyl-2-pyrazoline-5-one) (**1**) is a free-radical scavenger that is used as a treatment for cardiovascular diseases [2], as a neuroprotectant [3], and has been approved to treat amyotrophic lateral sclerosis (ALS) [4]. 4,4'-(Arylmethylene)bis(1-phenyl-3-methyl-1*H*-pyrazol-5-ol) derivatives have several biological activities and have been used as antiviral, antibacterial, anticancer and anti-inflammatory [5–9] compounds. Additionally, we recently found good anti-trypanosomatid activity of these compounds, which will be reported elsewhere.

Other derivatives of biological interest are the products obtained by nucleophilic addition of edaravone **1** to various acceptors (Scheme 1) [10]. When these acceptors are nitroalkenes, the corresponding Michael addition products are obtained, and the use of an asymmetric catalyst yields chiral pyrazol-3-ol derivatives [11–13]. A second Michael reaction with cinnamaldehyde allows the production of spiro[cyclohexanone-pyrazolones] in moderate to high yields with moderate to good diastereoselectivities and excellent enantioselectivities [14]. Similar spiro-pyrazolones can also be obtained when

pyrazolone **1** is treated with dibenzalacetones in the presence of an amine catalyst to afford spiro[cyclohexanone-pyrazolones] derivatives with high yields and high stereoselectivities. These spiro-derivatives are obtained by cascade [5 + 1] double Michael reactions [15].



**Scheme 1.** Different pyrazolone derivatives.

The equimolar reaction of **1** with  $\alpha,\beta$ -unsaturated trifluoromethyl ketones affords trifluoromethylated pyranopyrazoles after a tandem Michael addition/aromatization/cyclization reaction [16]. The same structure is obtained when **1** reacts with *trans*-cinnamaldehydes using diaryl prolinol silyl ethers as catalyst [17,18]. However, the reaction with a second molecule of cinnamaldehyde, using the same catalyst, affords spiro-pyrazolones through a Michael–Aldol cascade reaction [17,19,20]. The same reaction under NHC-catalyzed conditions, using chiral triazolium salt and  $\text{Na}_2\text{CO}_3$  as base, results in the enantioselective synthesis of dihydropyranone-fused pyrazole [21].

In all the above reactions, the addition of **1** occurs by a 1,4 addition; however, it is also possible, in the case of reactions with cinnamaldehydes, to have a 1,2 addition, which affords 4-aryllallylidenepyrazolone derivatives after a Knoevenagel condensation [21–23]. These condensates are similar in structure to 4-arylidene-pyrazolones, which are intermediates in the synthesis of 4,4'-(arylmethylene)bis(1-phenyl-3-methyl-1*H*-pyrazol-5-ols), and are formed by the equimolar reaction of 3-methyl-1-phenyl-2-pyrazoline-5-one with aromatic aldehydes [24], and among the different biological activities reported for 4-arylidene-pyrazolones, they also present antiparasitic activity [25].

Our laboratory has worked on the synthesis of heterocyclic compounds with possible antiparasitic activity [26,27], and in view of the great structural similarity that 4-aryllallylidenepyrazolones present versus 4-arylidene-pyrazolones, we attempted to synthesize several 4-aryllallylidenepyrazolone derivatives through the reaction of **1** with different

cinnamaldehydes. We report here the initial study of the synthesis of 4-arylallylidene-pyrazolones, using the reaction between 3-methyl-1-phenyl-2-pyrazoline-5-one (**1**) and 4-nitrocinnamaldehyde (**2**) as a model, as well as different catalysts and solvent conditions.

## 2. Methods

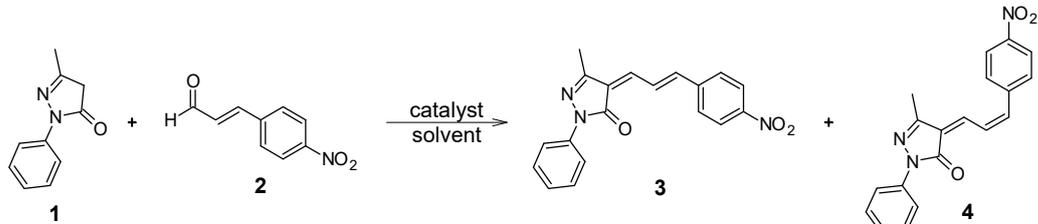
### 2.1. General

All solvents and reagents used in the investigation were from Sigma-Aldrich and were used without further purification. Melting points were determined on a Büchi Melting Point M-560 apparatus. The  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were recorded at 298 K on a BRUKER Ascend 500 MHz spectrometer using  $\text{CDCl}_3$  as the solvent. The photoisomerization was evaluated on an Oxford Instruments Pulsar benchtop NMR 60 MHz Spectrometer. Chemical shifts are expressed in ppm with TMS as an internal reference (TMS,  $\delta = 0$  ppm) for protons. The IR spectra were recorded with a VARIAN 660-IR/FT-IR spectrometer ( $4000\text{--}400\text{ cm}^{-1}$ ). Reactions were monitored by TLC on silica gel using chloroform and 1:4 ethyl acetate/hexane as the mobile phase, and compounds were visualized by UV lamp at 254 nm. Kinetic data were calculated in GraphPad Prism (GraphPad Software, San Diego, CA, USA).

### 2.2. General Procedure for the Synthesis of (4Z)-5-Methyl-4-[3-(4-nitrophenyl)-allylidene]-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **3** and **4**

To an equimolar solution of 4-nitrocinnamaldehyde (0.564 mmol) and edaravone (0.564 mmol) in 2.0 mL of solvent, 0.0564 mmol of catalyst were added and the mixture was stirred until the reaction was complete (Table 1). The solvent was evaporated under reduced pressure and the residue was dissolved with 2.0 mL of ethanol. Finally, with constant stirring, water was added to obtain 50% EtOH and the mixture was stored at 4 °C. The precipitates formed were collected by filtration, rinsed with cool 50% EtOH and dried under vacuum. After column chromatography on silica gel using chloroform as the eluent, **3** and **4** were obtained as pure products.

**Table 1.** Optimization of the Reaction Conditions.



Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%) <sup>1</sup>	Yield <b>3</b> (%) <sup>1</sup>	Yield <b>4</b> (%) <sup>1</sup>
1	—	THF	24 h	36	30	6
2	DABCO (10%)	EtOH	60	78	73	5
3	DABCO (10%)	THF	60	75	—	75
4	DABCO (10%)	$\text{CHCl}_3$	180	64	53	12
5	DABCO (10%)	Toluene	120	75	50	25
6	DABCO (10%)	$\text{Et}_2\text{O}$	120	39	23	16
7	DABCO (10%)	$\text{CH}_3\text{CN}$	120	75	—	75
8	DABCO (1%)	EtOH	90	71	50	21
9	DABCO (5%)	EtOH	90	72	48	24
10	DABCO (20%)	EtOH	60	78	56	22
11	—	EtOH	60	55	28	27
12	$\text{Et}_3\text{N}$ (10%)	EtOH	90	62	37	25
13	$\text{CH}_3\text{COONa}$ (10%)	EtOH	90	73	36	37
14	Pyridine (10%)	EtOH	90	33	32	1

Table 1. Cont.

Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%) <sup>1</sup>	Yield 3 (%) <sup>1</sup>	Yield 4 (%) <sup>1</sup>
15	FeCl <sub>3</sub> (10%)	EtOH	90	80	60	20
16	FeCl <sub>3</sub> ·6H <sub>2</sub> O (10%)	EtOH	120	84	66	18
17	HMTA (10%)	EtOH	90	44	42	2
18	L-Proline (10%)	EtOH	60	85	69	16
19	Morpholine (10%)	EtOH	90	46	40	6
20	Alopurinol (10%)	EtOH	180	41	38	3

<sup>1</sup> Determined by <sup>1</sup>H-NMR spectroscopy.

(4Z)-5-methyl-4-[(2E)-3-(4-nitrophenyl)-allylidene]-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**3**): Brown powder; mp: 216 °C–218 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 2.30 (s, 3H), 7.20 (dd, *J* = 11.6, 0.8 Hz, 1H), 7.20 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.24 (d, *J* = 15.7 Hz, 1H), 7.42 (dd, *J* = 8.5, 7.5 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.94 (dd, *J* = 8.8, 1.1 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 2H), 8.74 (dd, *J* = 15.7, 11.5 Hz, 1H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>) δ 12.9, 118.8, 124.4, 125.1, 127.0, 128.0, 129.0, 138.3, 141.6, 142.5, 145.1, 148.5, 149.5, 162.8. FTIR (cm<sup>-1</sup>): 1687, 1614, 1592, 1511, 1489, 1337, 1131, 977.3, 758.0.

(4Z)-5-methyl-4-[(2Z)-3-(4-nitrophenyl)-allylidene]-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**4**): Brown powder; mp: 217 °C–219 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 2.58 (s, 3H), 7.19 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.33 (d, *J* = 13.5 Hz, 1H), 7.42 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.54 (dd, *J* = 12.3, 0.8 Hz, 1H), 7.58 (dd, *J* = 13.4, 12.4 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.94 (dd, *J* = 8.7, 1.0 Hz, 2H), 8.29 (d, *J* = 8.8 Hz, 2H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>) δ 12.9, 118.7, 118.8, 124.4, 125.1, 127.1, 128.1, 128.7, 129.0, 138.3, 141.6, 142.5, 145.1, 149.5, 162.9. FTIR (cm<sup>-1</sup>): 1671, 1613, 1523, 1339, 1155, 1000, 838.3, 761.1.

### 2.3. Photoisomerization of **4**

A solution of **4** in CDCl<sub>3</sub> was irradiated with a blue LED light, and the isomerization was followed by <sup>1</sup>H-NMR. Data were analyzed with the statistical software Graph-Pad Prism.

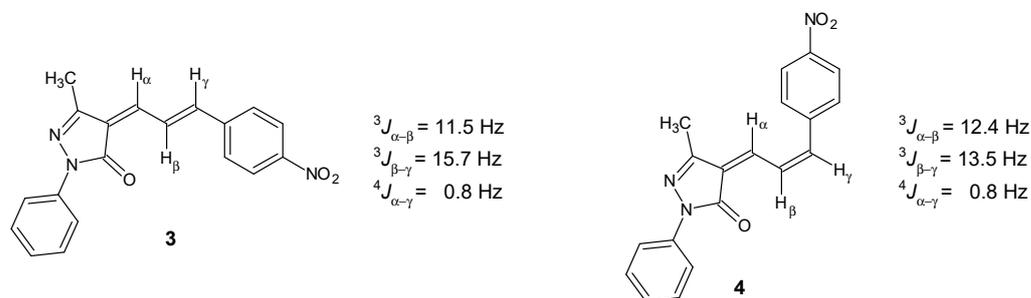
## 3. Results and Discussions

4-Arylallylidene-pyrazolones were synthesized using NaOAc as a catalyst, and acetic anhydride [23] and acetic acid [28] as the solvents under refluxing conditions. The uncatalyzed reaction under reflux conditions has also been reported [22]; however, the best yield was reported in the uncatalyzed reaction at room temperature using THF as solvent after 24 h of reaction [21].

We began our studies with 3-methyl-1-phenyl-2-pyrazolin-5-one (**1**) and 4-nitrocinnamaldehyde (**2**) as test substrates. When the reaction was carried out without the catalyst in THF, a 36% yield of product **3** was obtained after 24 h of reaction (Table 1, entry 1). However, when the reaction was performed with DABCO (10 mol%) as the catalyst at room temperature in EtOH (entry 2), the unsaturated pyrazolone **3** was obtained in 73% yield (based on <sup>1</sup>H-NMR spectroscopy) after 60 min of reaction. In addition, in both reactions the pyrazolone **4** was also obtained with 6% and 5% yields, respectively, and no evidence of the formation of a Michael adduct was observed.

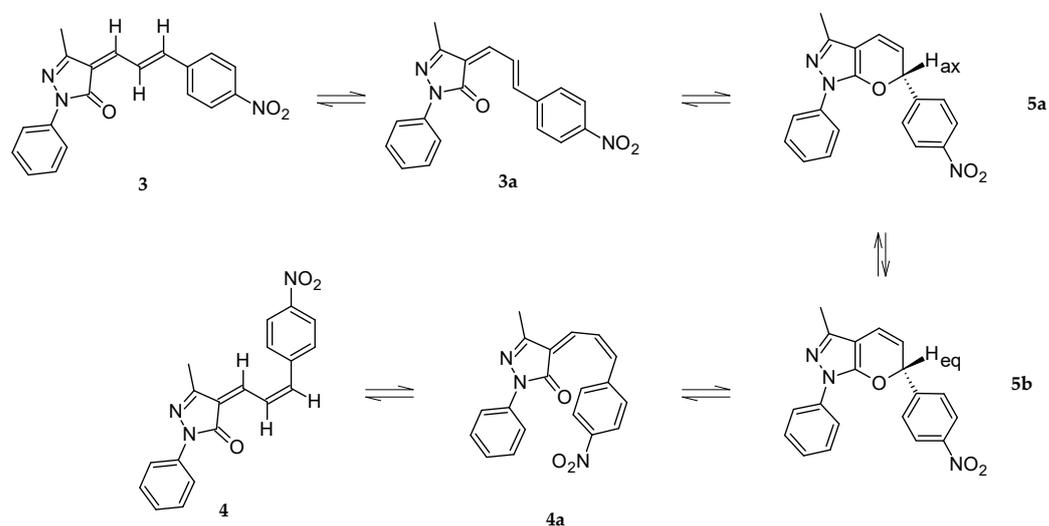
Spectroscopic analysis of **3** and **4** revealed that both compounds are the result of the Knoevenagel condensation of pyrazolone **1** to 4-nitrocinnamaldehyde; however, to our surprise, pyrazolone **4** exhibited a *cis* configuration at C2 instead of the *trans* configuration observed in **2** (Scheme 2). The <sup>1</sup>H-NMR spectrum of **3** is in agreement with the expected structure (Scheme 2). H<sub>β</sub> appears at 8.74 ppm and shows two couplings, H-H, <sup>3</sup>J<sub>β-α</sub> = 11.5 Hz and Hz and <sup>3</sup>J<sub>β-γ</sub> = 15.7 Hz, while H<sub>α</sub> and H<sub>γ</sub> appear at 7.20 and 7.24 ppm, respectively. These couplings show that the obtained isomer corresponds to *2E*. On the other hand, in the case of pyrazolone **4**, H<sub>β</sub> appears at 7.58 ppm and shows two couplings, H-H,

${}^3J_{\beta-\alpha} = 12.4$  Hz and  ${}^3J_{\beta-\gamma} = 13.5$  Hz. This proton shows an upfield shift of 1.16 ppm, possibly due to loss of conjugation owing to the conformation of the 2Z isomer.



**Scheme 2.** Coupling constant H-H of the unsaturated system of **3** and **4**.

The possible mechanism for the formation of the 4-arylallylidene pyrazolone **4** is depicted in Scheme 3. The Knoevenagel condensation of **1** with **2** affords **3** as the only regioisomer, as confirmed by 1D-NOESY. The 4-arylallylidene pyrazolone **3** is a 1-oxatriene that undergoes a reversible pericyclic oxa-6 $\pi$ -electrocyclization process until the 2H-pyran structure **5a** (valence isomerization) is obtained [29]. In **5a** the H $_{\gamma}$  is in an axial position, while in their conformer **5b**, it would be in an equatorial position. A second valence isomerization of **5b** allows the production of the pyrazolone **4**. Generally, compounds that have a 2H-pyran ring attached to an aromatic ring are stable enough to remain in the cyclic form (i.e., 2H-chromenes), otherwise, they tend to be unstable and prefer the opened isomeric form [30]. Likewise, simpler dienones, which could adopt a stable planar conformation, existed in the opened form. This is favored in the case of the 4-arylallylidene pyrazolones since they present an extended  $\pi$ -system [31]. Furthermore, no spectroscopic evidence of the formation of **5a** or **5b** was observed.



**Scheme 3.** Possible mechanism of the *cis-trans-cis* isomerization of **3** to **4**.

A kinetic study of the photoisomerization of a solution of **4** in  $\text{CDCl}_3$  was carried out, in which the solution was irradiated with a blue LED light and evaluated by  ${}^1\text{H-NMR}$ , observing that the half-life of **4** was 25 min, and at equilibrium 98.6% pyrazolone **3** was formed (Figure 1).

Different solvents were screened (entries 2–7) and it turned out that the highest total yield was obtained in EtOH. In all the evaluated solvents, both diastereomeric pyrazolones **3** and **4** were obtained, except in THF and acetonitrile, where only isomer **3** was formed, both with 75% yield. In the other solvents, the highest stereoselectivity was obtained in EtOH with a 14.6:1 diastereomeric ratio of **3** and **4**. Additional studies on the effect of

catalyst loading have shown that the best yield was observed with 10 mol%, yielding pyrazolones **3** and **4** with 78% yield (Table 1, entries 2, 8–10). Finally, using EtOH as a solvent, the effect of the catalyst on the reaction was evaluated (entries 11–20). In all cases, pyrazolone **3** was the main product. The uncatalyzed reaction produced a 55% yield with no stereoselectivity (entry 11), while FeCl<sub>3</sub> and *L*-proline were the best catalysts with 84% and 85% of total yields, respectively.

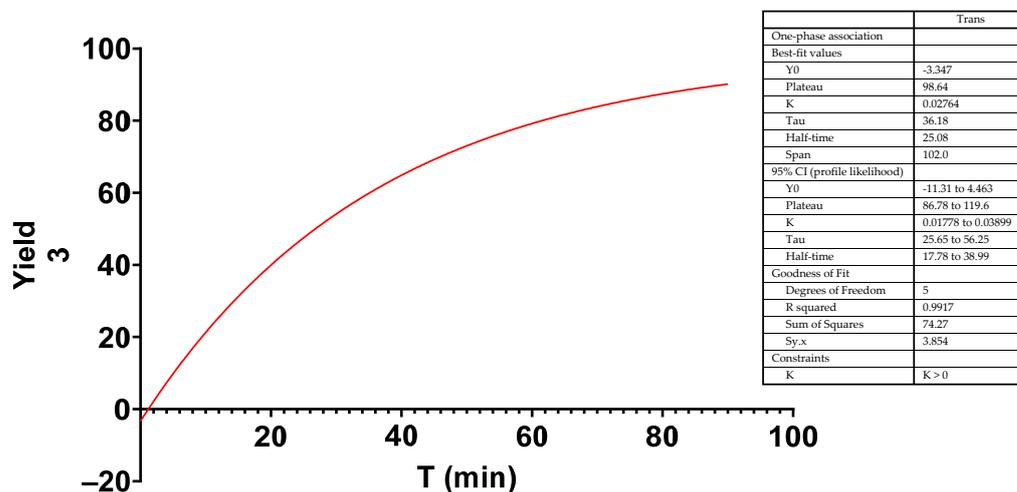


Figure 1. Yield of formation of **3** in CDCl<sub>3</sub> after photoisomerization of **4** at different times of irradiation.

#### 4. Conclusions

The synthesis of the (4*Z*)-5-methyl-4-[3-(4-nitrophenyl)-allylidene]-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one isomers **3** and **4** can be easily carried out through the Knoevenagel reaction between edaravone (**1**) and 4-nitrocinnamaldehyde (**2**). Both pyrazolones were formed in most of the solvents used; however, it can be observed that in protic solvents the diastereomeric ratio favored the pyrazolone **3** (2*E*), while in aprotic and nonpolar solvents, the formation of the pyrazolone **4** (2*Z*) was increased. In THF and acetonitrile the synthesis of **4** was stereospecific.

Finally, *L*-proline and FeCl<sub>3</sub> were the best catalysts, and with both, the diastereotopic ratio obtained was about 4:1; however, using DABCO in EtOH, good yield and a high diastereotopic ratio were obtained, which favored the synthesis of pyrazolone **3**.

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