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Synthesis of 4-Arylallylidenepyrazolones Derivatives †

Esteban Aguilar-Llanos [1], Juan Carlos Romero-Benavides [2] and Jorge Heredia-Moya [3,*]

[1] Facultad de Ciencias Químicas, Universidad Central del Ecuador, Quito 1705727, Ecuador; edavidallanos@gmail.com
[2] Departamento de Química, Universidad Técnica Particular de Loja, Loja 1101608, Ecuador; jcromerob@utpl.edu.ec
[3] Centro de Investigación Biomédica (CENBIO), Facultad de Ciencias de la Salud Eugenio Espejo, Universidad UTE, Quito 1705727, Ecuador; jorgeh.heredia@ute.edu.ec
* Correspondence: jorgeh.heredia@ute.edu.ec; Tel.: +593-2-2990800 (ext. 2538)

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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-Arylidenepyrazolones derivatives also have antiparasitic activity and are intermediates in the synthesis of these bispirazoles 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 want to synthesize several 4-arylallylidenepyrazolones derivatives through the reaction of pyrazol-3-one with different cinnamaldehydes. We report here the study of the synthesis of some 4-arylallylidenepyrazolones 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 $FeCl_3$ are the best catalysts, and also we observed a solvent effect in the reaction. Our preliminary results indicate that aprotic solvents favor the formation of the 2*Z* isomer instead of the 2*E* isomer.

Keywords: pyrazoles; 4-arylallylidenepyrazolones; cinnamaldehydes; valence isomerization

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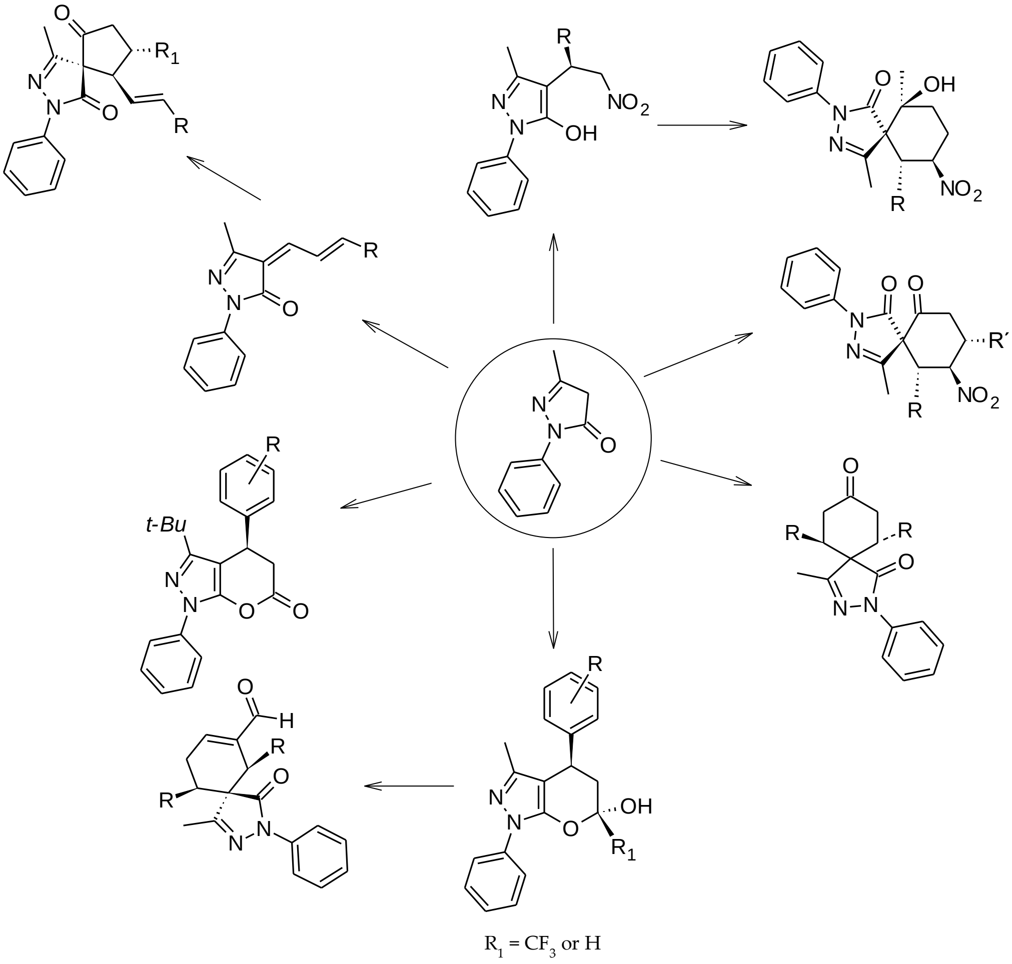
1. Introduction

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, 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 used as treatment for cardiovascular diseases [2], as 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 and will be reported elsewhere.

Other derivatives of biological interest are the products obtained by nucleophilic addition of edaravone **1** to various acceptors (**Error! Reference source not found.**) [10]. When these acceptors are nitroalkenes, the corresponding Michael addition products are obtained, and the use of asymmetric catalyst yields chiral pyrazol-3-ol derivatives [11–13]. A second Michael reaction with cinnamaldehyde allows to obtain spiro[cyclohexanone-pyrazolones] in moderate to high yields with moderate to good diastereoselectivities and excellent enantioselectivities [14]. Similar spiropyrazolones can also be obtained when pyrazolone **1** was treated with dibenzalacetones in the presence of 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.

Equimolar reaction of **1** with α,β-unsaturated trifluoromethyl ketones afford 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, afford spyropyrazolones through a Michael–Aldol cascade reaction [17,19,20]. The same reaction under the NHC-catalyzed conditions, using chiral triazolium salt and Na_2CO_3 as base, result 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, the addition 1,2, which afford 4-arylallylidenepyrazolones derivatives after Knoevenagel condensation [21–23]. These condensates are similar in structure to 4-arylidenepyrazolones 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-arylidenepyrazolones, they also present anti-parasitic activity [25].

Our laboratory has worked on the synthesis of heterocyclic compounds with possible anti-parasitic activity [26,27] and in view of the great structural similarity that 4-

arylallylidenepyrazolones present versus 4-arylidenepyrazolones, we want to synthesize several 4-arylallylidenepyrazolones derivatives through the reaction of **1** with different cinnamaldehydes. We report here the initial study of the synthesis of 4-arylallylidenepyrazolones, using the reaction between 3-methyl-1-phenyl-2-pyrazoline-5-one (**1**) and 4-nitrocinnamaldehyde (**2**) as model, using different catalyst 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}H and ^{13}C NMR spectra were recorded at 298 K on a BRUKER Ascend 500 MHz spectrometer using $CDCl_3$ as solvents. 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 (4000–400 cm^{-1}). The ^{19}F-NMR spectra were acquired on an Oxford Instruments Pulsar benchtop NMR 60 MHz Spectrometer (Tubney Woods, Abingdon, Oxford, UK). Reactions were monitored by TLC on silica gel using chloroform and 1:4 ethyl acetate/hexane as 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 eluent, **3** and **4** were obtained as pure products.

(4*Z*)-5-methyl-4-[(2*E*)-3-(4-nitrophenyl)-allylidene]-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (3): Brown powder; mp: 216 °C–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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^{-1}): 1687, 1614, 1592, 1511, 1489, 1337, 1131, 977.3, 758.0.

(4*Z*)-5-methyl-4-[(2*Z*)-3-(4-nitrophenyl)-allylidene]-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (4): Brown powder; mp: 217 °C–219 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 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 (d, *J* = 11.6 Hz, 1H), 7.58 (dd, *J* = 13.2, 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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^{-1}): 1671, 1613, 1523, 1339, 1155, 1000, 838.3, 761.1.

2.3. Photoisomerization of **4**

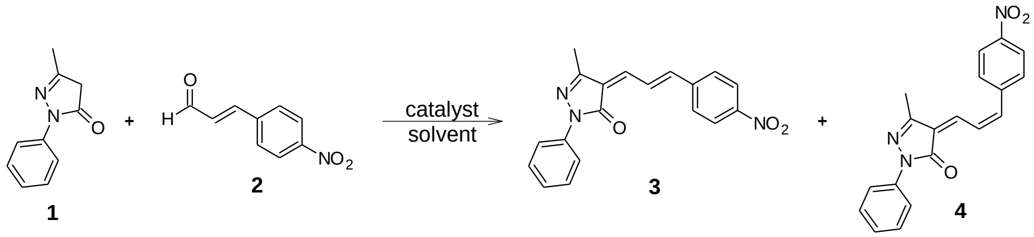
A solution of **4** in $CDCl_3$ was irradiated with a blue LED light y the isomerization was followed by ^{1}H-NMR. Data were analyzed with the statistical software GraphPad Prism.

3. Results and Discussions

4-Arylallylidenepyrazolones have been synthesized using NaOAc as catalyst using acetic anhydride [23] and acetic acid [28] as 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 started 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 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 done with DABCO (10 mol%) as catalyst at room temperature in EtOH (entry 2), the unsaturated pyrazolone **3** was obtained in 73% yield (based on ^{1}H NMR spectroscopy), after 60 min of reaction. In addition, in both reactions the pyrazolone **4** was also obtained with 6% and 5% yield respectively, and no evidence of the formation of Michael adduct was observed.

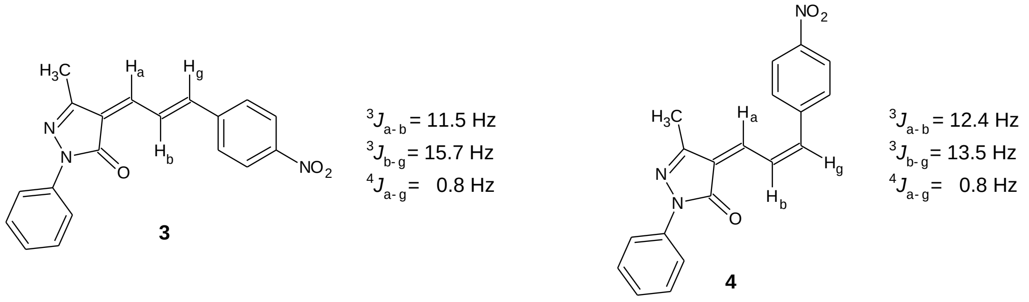
Table 1. Optimization of the Reaction Conditions.



Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%)[1]	Yield 3 (%) [1]	Yield 4 (%) [1]
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%)	$CHCl_3$	180	64	53	12
5	DABCO (10%)	Toluene	120	75	50	25
6	DABCO (10%)	Et_2O	120	39	23	16
7	DABCO (10%)	CH_3CN	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	Et_3N (10%)	EtOH	90	62	37	25
13	CH_3COONa (10%)	EtOH	90	73	36	37
14	Pyridine (10%)	EtOH	90	33	32	1
15	$FeCl_3$ (10%)	EtOH	90	80	60	20
16	$FeCl_3,6H_2O$ (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

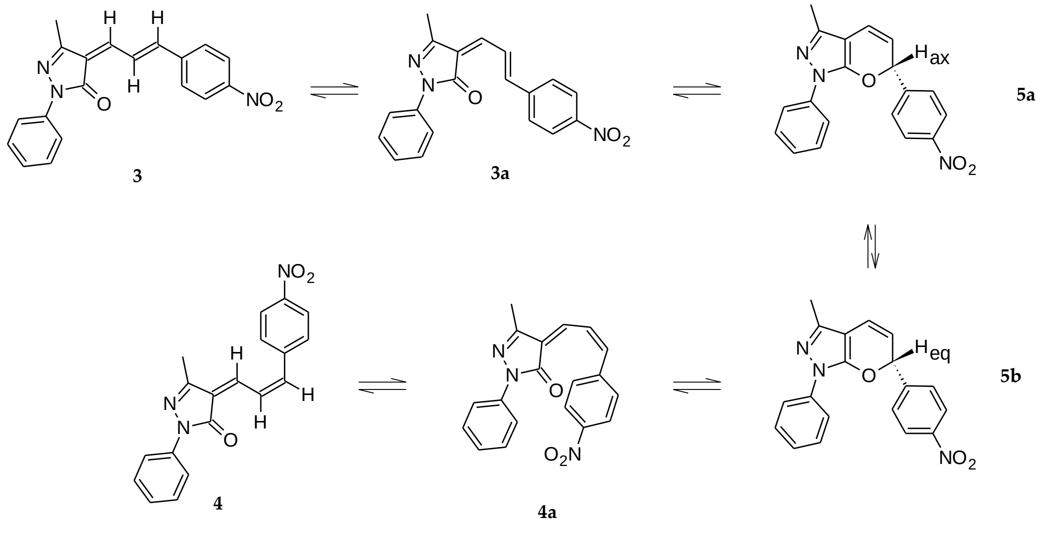
[1] Determined by ^{1}H NMR spectroscopy.

Spectroscopic analysis of **3** and **4** reveals that both compounds are the result of the Knoevenagel condensation of pyrazolone **1** to 4-nitrocinnamaldehyde, however, to our surprise, pyrazolone **4** exhibits a *cis* configuration at C2 instead of the *trans* configuration observed in **2** (Scheme 1). The ^{1}H-NMR spectrum of **3** is in agreement with the expected structure (Scheme 1). Hβ appears at 8.74 ppm and shows two couplings H-H, $^{3}J_{\beta\text{-}\alpha} = 11.5$ Hz y $^{3}J_{\beta\text{-}\gamma} = 15.7$ Hz, while Hα and Hγ appear at 7.20 and 7.24 ppm respectively. These couplings show that the isomer obtained corresponds to 2*E*. On the other hand, in the case of pyrazolone **4**, Hβ appears at 7.58 ppm and shows two couplings H-H, $^{3}J_{\beta\text{-}\alpha} = 12.4$ Hz y $^{3}J_{\beta\text{-}\gamma} = 13.2$ Hz. This proton shows an upfield shift of 1.16 ppm, possibly due to loss of conjugation owing to the conformation of the 2*Z* isomer.



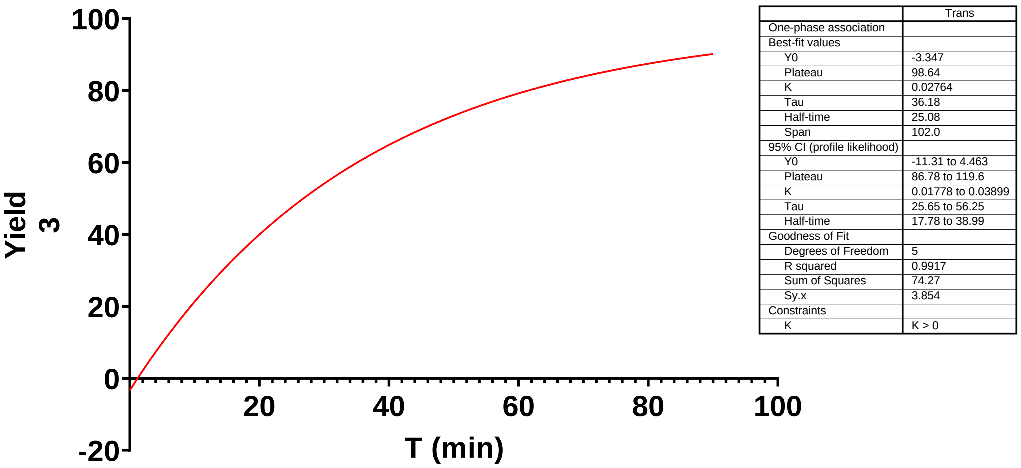
Scheme 1. Coupling constant H-H of the unsaturated system of **3** and **4**

The possible mechanism for the formation of the 4-arylallylidenepyrazolone **4** is depicted in **Error! Reference source not found.**. The Knoevenagel condensation of **1** with **2** affords **3** as the only regioisomer, confirmed by 1D-NOESY. The 4-arylallylidenepyrazolone **3** is a 1-oxatriene that undergoes a reversible pericyclic oxa-6π-electrocyclization process until the 2*H*-pyran structure **5a** (valence isomerization) [29]. In **5a** the Hγ is in an axial position, while in their conformer **5b**, it would be in an equatorial position. A second valence isomerization of **5b** allows to obtain the pyrazolone **4**. Generally, compounds that have a 2*H*-pyran ring attached to an aromatic ring are stable enough to remain in the cyclic form (i.e., 2*H*-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-arylallylidenepyrazolones since they present an extending π-system [31]. Furthermore, no spectroscopic evidence of the formation of **5a** or **5b** is 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 $CDCl_3$ was made for this, the solution was irradiated with a blue LED light and it was evaluated by ^{1}H-NMR, observing that the half-life of **4** is 25 min, and at equilibrium 98.6% pyrazolone **3** is formed (**Error! Reference source not found.**).



	Trans
One-phase association	
Best-fit values	
Y0	-3.347
Plateau	98.64
K	0.02764
Tau	36.18
Half-time	25.08
Span	102.0
95% CI (profile likelihood)	
Y0	-11.31 to 4.463
Plateau	86.78 to 119.6
K	0.01778 to 0.03899
Tau	25.65 to 56.25
Half-time	17.78 to 38.99
Goodness of Fit	
Degrees of Freedom	5
R squared	0.9917
Sum of Squares	74.27
Sy.x	3.854
Constraints	
K	K > 0

Figure 1. Yield of formation of **3** in $CDCl_3$ after photoisomerization of **4** at different time of irradiation.

Different solvents were screened (entries 2–7) and it turned out that the highest total yield is obtained in EtOH. In all solvents evaluated, 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 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 produces a 55% yield with no stereoselectivity (entry 11), while $FeCl_3$ and *L*-proline were the best catalysts with 84% and 85% of total yields respectively.

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 solvents used, however, it can be observed that in protic solvents the diastereomeric ratio favors the pirazolone **3** (2*E*), while in aprotic and nonpolar solvents, increase the formation of the pirazolone **4** (2*Z*). In THF and acetonitrile the synthesis of **4** was stereospecific.

Finally, *L*-proline and $FeCl_3$ are the best catalysts, and with both, the diastereotopic ratio obtained is about 4:1, however, using DABCO in EtOH, good yield and high diastereotopic ratio are obtained, which favors the synthesis of pyrazolone **3**.

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

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