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The mechanism of the reaction of hydrazines with α,β-unsaturated carbonyl compounds to afford hydrazones and 2-pyrazolines (4,5-dihydro-1*H*-pyrazoles): Experimental and theoretical results

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ABSTRACT

The reaction of hydrazines with α,β-unsaturated carbonyl compounds to afford 2-pyrazolines was studied using a dissymmetric chalcone (phenyl/*p*-tolyl) and three hydrazines, hydrazine itself, phenylhydrazine and thiosemicarbazide. Several products were identified, and some reaction paths established thanks to the evolution of ^{1}H and ^{13}C NMR spectra with time. Theoretical calculations on energies and chemical shifts were of paramount importance to ascertain the structure of some products. For important steps, the transition states were calculated while IRCs proved necessary to find some unexpected intermediates.

1. Introduction

The reaction of hydrazines with 1,3-difunctional compounds is the way to a wide variety of pyrazole derivatives (Scheme 1) [1]. Although pyrazoles (in blue) are more common than pyrazolines (in red), in what concerns the mechanisms, those of pyrazoles and pyrazolines are similar with the difference than in pyrazoles the hydroxy group is eliminated in form of water from the 5-hydroxypyrazolines [2].

The reactions of Scheme 1 are general and can be extended in two directions: first, hydrazine can be replaced by hydroxylamine to afford isoxazoles [3], then by other diamino derivatives like *o*-phenylenediamine (1,5-benzodiazepines) [4] and 1,8-diaminonaphthalenes (perimidines) [5] and by a combination of both modifications as an entry, for instance, of benzothiazepines [6].

As most heterocycles, 2-pyrazolines have applications in the fields of drugs and materials [7,8]; in the three most used databases we found the words "pyrazoline" and "dihydropyrazole" cited respectively in Google Scholar 27.600 and 3.390, in Scifinder 10.604 and 1.370 and in the Web of Science 4.526 and 362 times (approximately between 8 and 12 times more of "pyrazolines" than of "dihydropyrazoles"). These numbers, although only indicative, prove the general importance of pyrazolines.

To summarize the results on the mechanism of the reaction of hydrazines with α,β-unsaturated carbonyl compounds to afford 2-pyrazolines, we decided to anticipate in Scheme 2 part of our results.

In the already cited publication of 1970 we discussed the four possibilities of Scheme 2 resulting from two kinds of additions, 1,2 and Michael, and the different nitrogen atoms NH and NH_2, obviously for hydrazine both nitrogen atoms are identical [1]. We have previously demonstrated that when a hydrazone **7** bear an electron-withdrawing substituent (EWG, in this case a 2′,4′-dinitrophenyl group **4d**), the hydrazone needs very strong conditions to cyclize into the pyrazoline **1**, *i.e.*, boiling in a mixture AcOH/BrH [9]. We observed that the Michael adduct **12b** reacts with another molecule of phenylhydrazine to yield a phenylhydrazone-phenylhydrazine **15b** [10]. If an α,β-unsaturated carbonyl compound with substituents about the CC double bond more alike than in chalcones, where the *E* isomer is much more stable than the *Z* one, such as 3-ethyl-3-pentene-2-one, we proved that there is no relationship between the *E/Z* isomerism of the CC double bond and the *cis/trans* isomerism of the substituents at position 4 and 5 in the pyrazoline [11].

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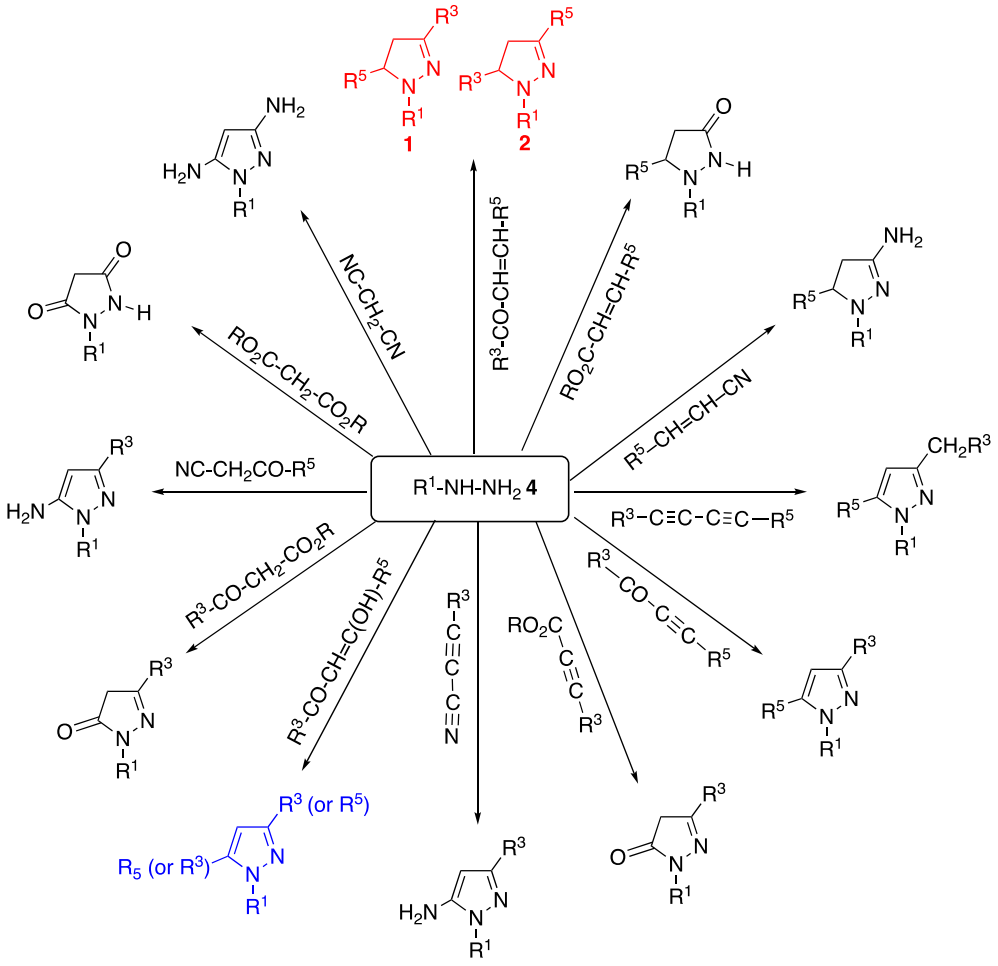
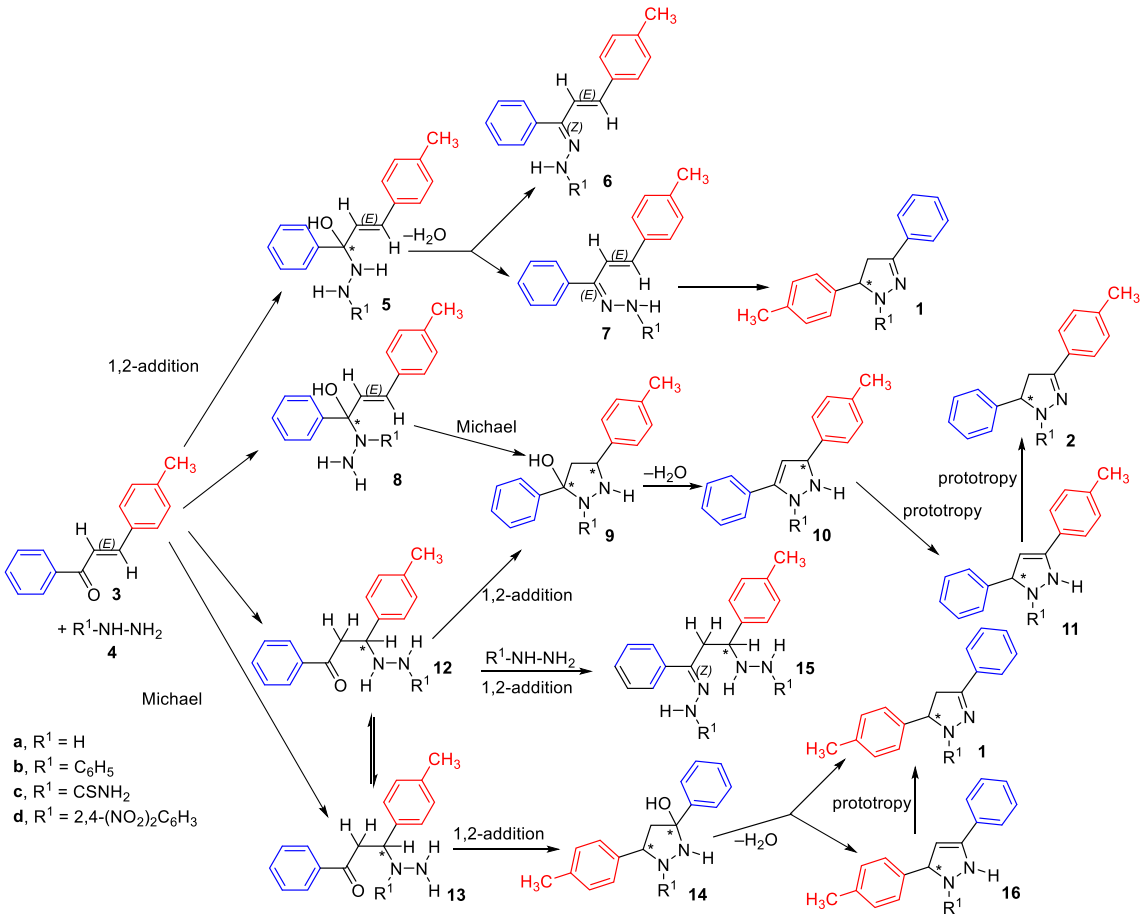


Scheme 1. Structures obtained (all known) from monosubstituted hydrazines (including $R^1 = H$) and 1,3-difunctional compounds. In blue, pyrazoles (two isomers) obtained from β-dicarbonyl compounds and in red the isomeric 2-pyrazolines **1** and **2**.

Elsewhere, the mechanism of the reaction of 1,2-disubstituted hydrazines with α,β-unsaturated carbonyl compounds has been studied [10]. When using 1-methyl-2-phenylhydrazine, the structure of the resulting 3-pyrazoline proves that the Michael addition takes place by the NHMe and not by the NHPh group, consequently, in the case of phenylhydrazine (**4b**) the Michael addition should afford **12b** and not **13b** (the same for **12c**) although the effect of the *N*-methyl group may render its nitrogen atom more reactive than that of the NH_2 of phenylhydrazine. Finally, we proposed that the **7** to **1** step corresponds to an electrocyclic mechanism [12].

From a long time there were no new publications dealing with the mechanisms of Scheme 2. Then in 1986, Kenny and Robinson published two important papers (preliminary −1986- but more complete in NMR data and full −1987- with kinetic results) [13,14]. To distinguish both phenyl groups they labeled specifically each one of the three carbon atoms of the CO−CH=CH bridge and, to use $^{13}C-^{15}N$ spin-spin coupling constants, they carried out the reaction with a double labeled ^{15}N-phenylhydrazine (**4b**^{15}). We will use the same numbering than in Scheme 2 but now that there is no CH_3 substituent but different ^{13}C isotopomers, we will add an * to the number. They identify **1b***, **12b***, **13b***, **14b*** and **15b***; besides, they explain that hydrazone **7b*** cannot cyclize into pyrazoline **1b*** because it is forbidden by Baldwin's rules [15]. Compound **13b*** was not observed; according to the authors it cyclizes quickly to **14b***. Müller and List [16] (not citing Kenny and Robinson) doubt about the use of Baldwin's rules and prefer, like Rolf Huisgen [17] and us [1], to use Woodward-Hoffmann rules to describe the reaction as a forbidden pericyclic 6π-electrocyclization [18]. In summary, the reaction of **3*** with Ph-^{15}NH−^{15}NH$_2$ (**4b**^{15}) start with Michael addition to afford both adducts **12b***^{15} and **13b***^{15} (not observed); **13b***^{15} through hydroxypyrazoline **14b***^{15} afford the pyrazoline **1b***^{15}; adduct **12b***^{15} yield the double condensation product, **15b***^{15}, then the reaction stopped and the sequence **12b***^{15} → **9b***^{15} → **10b***^{15} → **11b***^{15} → **2b***^{15} was not observed.

A series of papers by Brière et al. [19,20] studied the reaction of a series of hydrazines where R^1 is an EWG, amongst them the $CSNH_2$ group (**c** series) with a series of chalcones with both phenyl groups being different but none like **3**, the closer are a 2-MeC_6H_4 and 4-ClC_6H_4 (denoted with an apostrophe mark, e.g., 3′); they called aza-Michael the step we have called Michael (Scheme 2). Although



Scheme 2. General representation of the possible reactions.

the complete study was carried out with acetohydrazide ($R^1 = COCH_3$), we will discuss their results as if they correspond to the **c'** series (incomplete). They carried out the reactions in the presence of a very strong base (TBD, 1,5,7-triazabicyclo [4.4.0]dec-5-ene) that results in the reacting species being the $CH_3CO–N^{(-)}$-NH_2 and the observed sequence is **3'** + **4c**$^{(-)}$ → **13c**$'^{(-)}$ followed by protonation to continue as → **14c'** → **1c'** (**3**′ are chalcones other than **3**). TDB also facilitates the isomerization of the Michael product, **12c**′ into its isomer **13c**′ by deprotonation of the acetohydrazide to yield $CH_3CO–N^{(-)}NH_2$ that reacts by the $N^{(-)}$ to affords, after protonation, **13c'**. This proves that the normal addition, *i.e.*, by the NH_2, of acetohydrazide on chalcones to yield **12** is reversible but not that the same is true for **13**. Theoretical calculations of protonation and deprotonation indicate that in neutral thiosemicarbazide **4c** the N atom of the NH_2 is more basic than that of the NH group by 63.5 kJ mol^{-1} while in thiosemicarbazide anions that corresponding to the NH [H_2N-CS-$N^{(-)}$-NH_2] is more stable than that corresponding to the NH_2 [H_2N-CS-NH-$NH^{(-)}$] by 98.0 kJ mol^{-1}.

A recent paper proposed tentatively a **5** → **14** → **1** sequence without experimental proofs [21]. Finally in what concerns the reactivity of both nitrogen atoms in hydrazines there is an abundant bibliography that the more nucleophilic is the NH in methylhydrazine **4a** [1,2] and the NH_2 in phenylhydrazine **4b** [1,2,14,16], thiosemicarbazide **4c** [20b] and 2.4-dinitrophenylhydrazine **4d** [22].

In what concerns experimental NMR data of ^{1}H and ^{13}C of both hydrazones and pyrazolines the most relevant information is reported in several publications, some of them of our group [23–27].

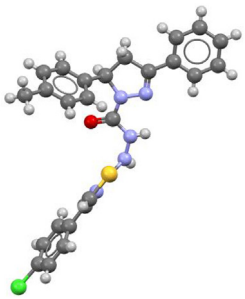
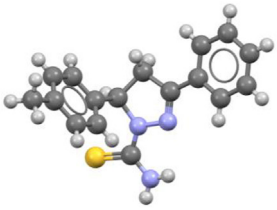
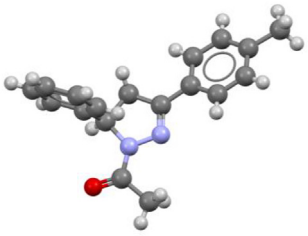
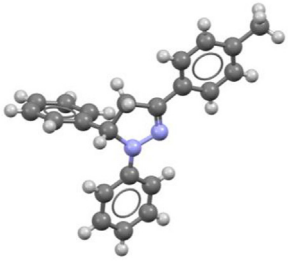
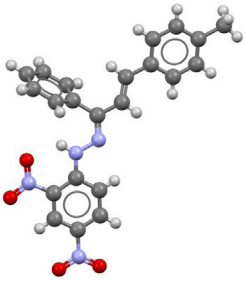
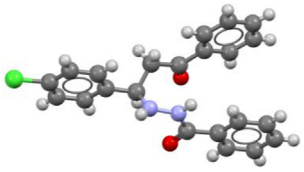
A search in the Cambridge Structural Database (CSD) [28] for X-ray structures of compounds reported, or closely related to them, obtained from methyl chalcone: **1a**, **2a**, **7a**, **12a**, **1b**, **2b**, **7b**, **12b**, **13b**, **1c**, **12c** and any derivative of the **d** series (*N*-2,4-dinitrophenyl) affords a very small number of items all of them recent (2011–2014) or very recent (2017–2020) that are reported in Table 1.

Only the structures of **2b** and **6d** have been reported; structures related to **1c** are DAZCEP (but with a C=O instead of a C=S), KOGDAO and YUKDAM that are coinage metal complexes of **1c**; finally, UNEGOK has a *p*-Cl substituent instead of a *p*-CH_3 group and a benzoyl group instead of carbothioamide one.

2. Results and discussion

We decided to use as an α,β-unsaturated carbonyl compound, a chalcone like in most studies on the reaction that we have reported

Table 1
X-ray molecular structures of 2-pyrazolines and hydrazones of the present paper or related to them.

		
DAZCEP [29] related to **1c**	KOGDAO [30] & YUKDAM [31] **1c** linked by the $CSNH_2$ to Ag	QERVEP [32] **1c** linked by the S to Au^+
		
VIVHEP [33] **2b**	MEXLIN [24b] **6d**	UNEGOK [34] related to **12c**

previously. It is fundamental to differentiate both phenyl groups, otherwise several structures will become identical if $R^3 = R^5$ (Scheme 1); to label chalcone a methyl group in *para*-position was selected to avoid steric effects and to minimize electronic ones, in the present work the methyl group was placed on the styrenic phenyl ring ($R^5 = p$-CH_3-C_6H_4). However, in some cases literature results were available only for chalcone itself ($R^5 = C_6H_5$); for these results an * was added, e.g. **7c*** is the *E-E* thiosemicarbazone of chalcone (including its ^{13}C isotopomers).

Three hydrazines were used: hydrazine, phenylhydrazine and thiosemicarbazide; the last one to decrease the reactivity of the nitrogen of the NH group. Literature results of the **d** series will be used when necessary.

The methodology was to follow the reaction in an NMR tube inside the cavity of a 400 or 500 MHz spectrometer at regular intervals of 15 min for 15 h and for 24 h afterwards. 0.1 mmol of **3** and **4** were dissolved in 0.6 mL of solvent ($CDCl_3$ or DMSO-d_6) and glacial acetic acid (20 μL) or potassium hydroxide (0.1 mmol) were added. The selectivity of the pyrazolines was deduced by NOE experiments by irradiation at the frequency of H-5. In all cases a NOE was observed for H-4 and phenyl or *p*-tolyl-5.

Afterwards, a small section about the stability of 3-pyrazolines and a large one of the theoretical study (energies and NMR) of the same reactions reported in Section 2.1.

2.1. NMR studies of the reactivity

2.1.1. Hydrazine (*4a*)

Reaction of **3** with hydrazine hydrate **4a** (R^1 = H) in acidic conditions showed the appearance of the intermediate Michael addition product (**12**–**13**)**a** together with the pyrazolines **1a** and **2a** produced by evolution of (**12**–**13**)**a**. Signals were determined by COSY experiments and the regiochemistry by 1D and 2D NOE experiments. It is remarkable that **1a** is the major product and it appears from the beginning of the kinetic experiment. A small doublet at 6.06 ppm can be assigned to the hydrazone (see Fig. 1).

In basic conditions in DMSO-d_6 different results were obtained (see Fig. 2). Addition of hydrazine hydrate **4a** produces the appearance of two new products that evolve to **1a** in 6 h. These products were characterized as the cyclic diastereomeric aminals **14a**. NOESY experiments show the interchange between these two intermediates in equilibrium with the open intermediate **13a**. HMBC experiments indicate the absence of a long-range correlation of H-4 with any carbonyl or imine carbon but with carbons at 90 ppm, characteristics of the aminal carbon of **14a**.

2.1.2. Phenylhydrazine (*4b*)

Reaction of **3** with phenylhydrazine **4b** in acidic conditions showed the slow appearance of the intermediate Michael addition products **12b** and **13b** that evolved slowly again to pyrazolines **1b** and **2b** (see Fig. 3). **1b** was isolated in a preparative experiment and characterized by NMR spectroscopy. Signals of the pyrazoline ring of **1b** and **2b** and of the alkyl chain in **12b** and **13b** were assigned by COSY experiments and the regiochemistry was inferred by 1D and 2D NOE experiments showing the NOE with the *ortho* proton of the *p*-tolyl and phenyl groups with H-5 of the pyrazoline ring of **1b** and **2b** respectively and with H-3 of the alkyl chain in **12b** and **13b**. It should be remarked the presence of a large amount of hydrazone

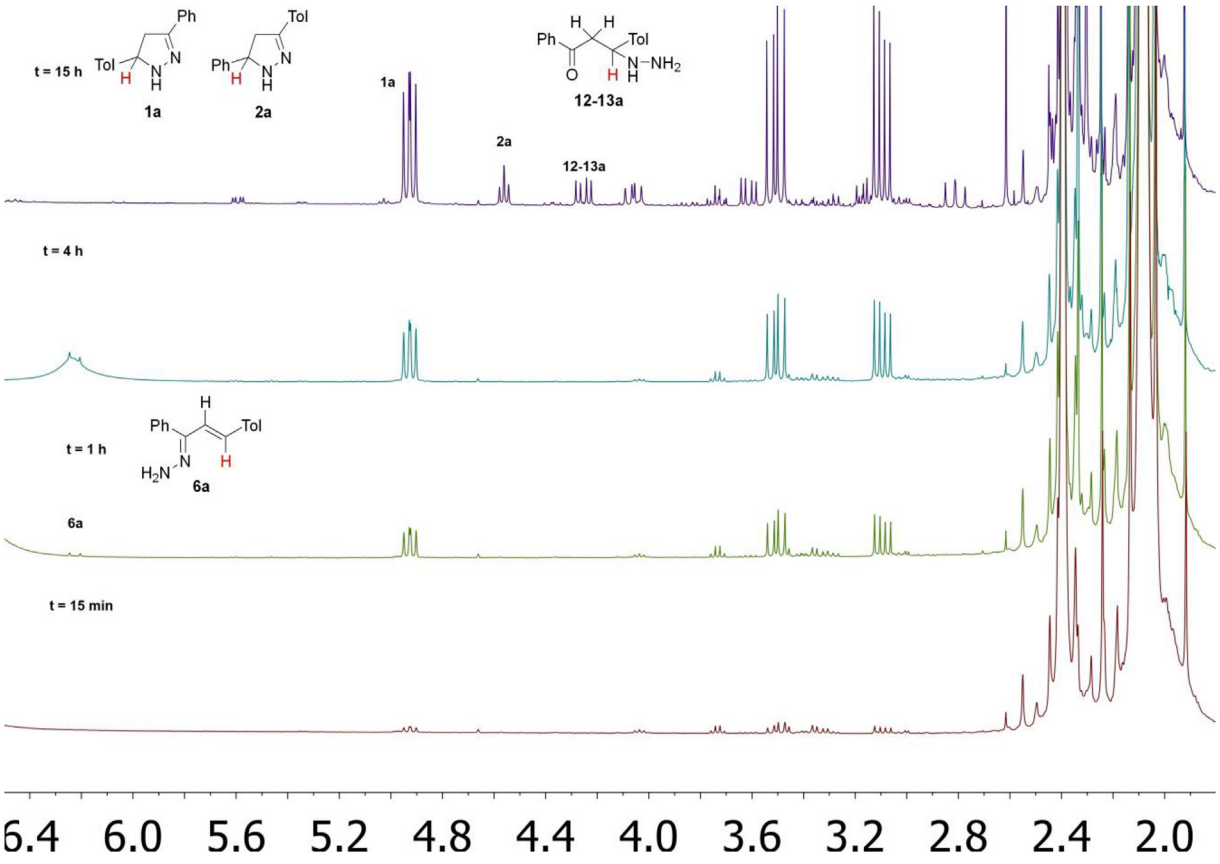


Fig. 1. Reaction of **3** with hydrazine hydrate **4a** in the NMR tube. Solvent $CDCl_3$; AcOH (cat). In red, protons pointed out in the spectrum.

6b or **7b** that does not evolve within time to the pyrazoline **1b**.

In basic conditions important changes were observed (see Fig. 4). Hydrazones **6** or **7b** were not observed; pyrazoline **1b** was detected but not the corresponding Michael addition product **13b** probably due a rapid cyclization to the pyrazoline. On the contrary Michael addition product **12b** was observed but not the pyrazoline **2b**, probably because the evolution from **9** to **2b** is not favored in basic conditions.

2.1.3. Thiosemicarbazide (*4c*)

Reaction of **3** with thiosemicarbazide **4c** in acidic conditions does not produce any results probably due to the low reactivity of **4c**. In consequence, reactions were performed in basic conditions to enhance the nucleophilicity of **4c** by deprotonation. In the first experiment a signal at 5.33 ppm was observed and it is slowly transformed to the signal at 6.04 ppm that corresponds to the pyrazoline **1c** that was characterized in a preparative experiment by comparison with the described products and NOE experiments. Considering this transformation and NOE experiments the structure of **13c** was assigned. It should be remarked that pyrazoline **2c**, Michael product **12c** and thiosemicarbazones **6** and **7** were not detected (see Fig. 5).

2.2. Theoretical calculations

2.2.1. Energetics results

2.2.1.1. Isolation of 3-pyrazolines, literature results. One of the intriguing aspects of Scheme 2 concerns the transformation **10** → **2**. Compound **10** is a 3-pyrazoline that some authors called a 4-pyrazoline numbering the ring from the N-substituted atom. The stability, in the sense of the reason why 3-pyrazolines do not isomerize into 2-pyrazolines, is summarized in Scheme 3.

1,2-disubstituted 3-pyrazolines **17** and 3,3′- disubstituted 3-pyrazolines **18** cannot isomerize into 2-pyrazolines; 2,3,3-tribstituted-3-prazolines **19** isomerize to 2-pyrazolines **21**, the R^3 substituents can be H or different from H, the process corresponds to an enamine/imine [35] or enehydrazine/hydrazone [36] tautomerization. The most important result is the transformation **20** → **22** that it is equivalent to **10** → **2** (Scheme 2); **10** has never been isolated nor detected in any of the publications cited previously. Both steps in the processes **20** → **23** → **22** (model compounds) and **10** → **11** → **2** (Scheme 2) are 1,3-sigmatropic shifts that are forbidden by symmetry [37]. The difference is that the first step is a classical CH to C process while the second step is a NH to C process and this can modify the barriers of proton transfer.

In acid-catalyzed conditions, since protonation of 3-pyrazolines affords 2-pyrazolinium cations [38], the mechanism through **27** allows to transform **25** into **26** (Scheme 4).

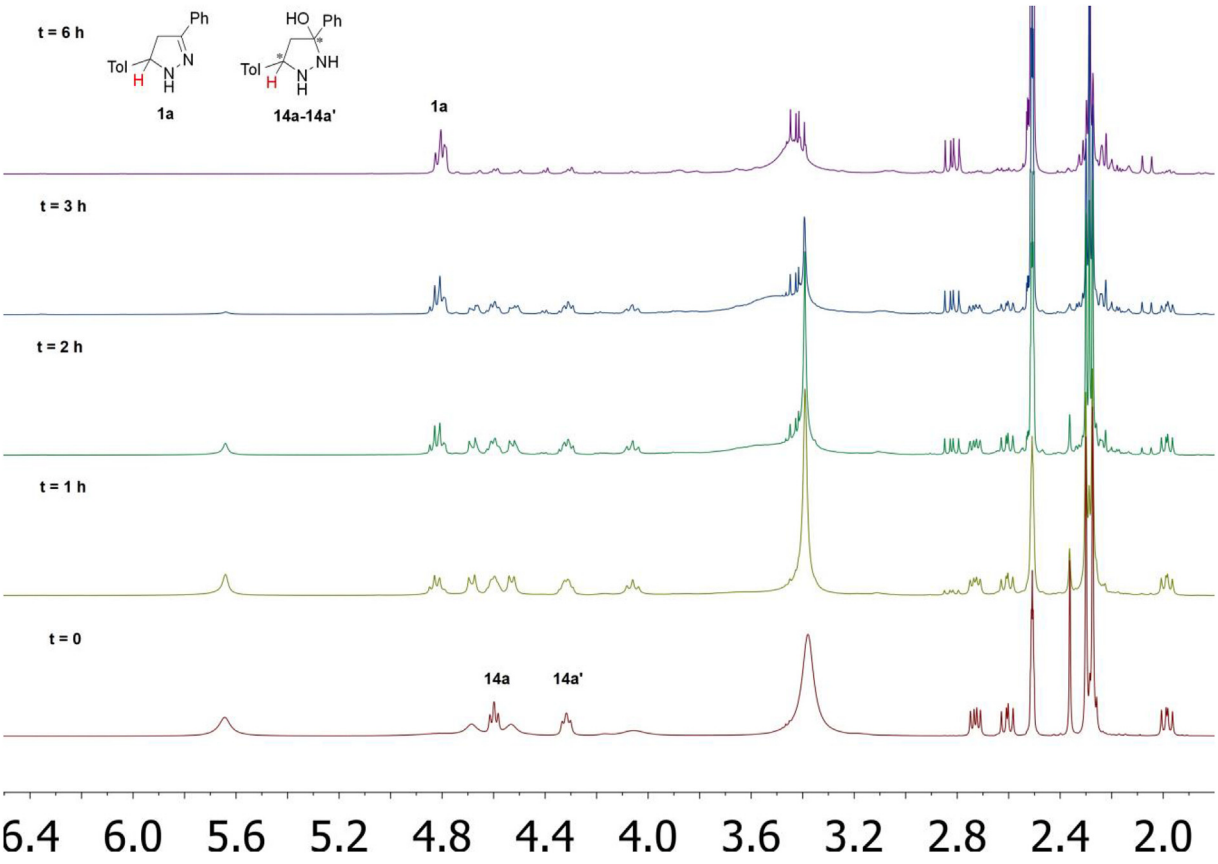


Fig. 2. Reaction of **3** with hydrazine hydrate **4a** in the NMR tube. Solvent DMSO-d_6; KOH. In red, protons pointed out in the spectrum.

We have calculated both processes and the results are given in Table 2; the sequence **24** → **25** → **26** corresponds to the sequence **20** → **23** → **22** for $R^1 = CH_3$ and $R^3 = H$ (in all, five H atoms besides those of the methyl group). When the **24** → **25** → **26** and **10a** → **11a** → **2a** sequences were explored using IRC (Intrinsic Reaction Coordinate) calculations it was discovered that there are two intermediates between the molecules that we have called **int24** and **int25** on one hand and **int10a** and **int11a** on the other (Scheme 5). These intermediates are high-energy zwitterions (ZW) (Fig. 6).

Both profiles are very similar (statistically identical, intercept = 0, slope = 1, $R^2 = 0.99$). In the chalcone derivatives (**24**–**25**-**26**), both 3-pyrazolines are very similar in energy because the only difference is the position of the *para*-methyl group; the 2-pyrazolines are more stable than the 3-pyrazolines. The ZW intermediates are very high in energy, 280–290 kJ mol^{-1}, as are all the TSs. Therefore, both steps are forbidden and in neutral conditions and the 3-pyrazolines should be stable.

A series of authors reported 3-pyrazolines with structures related to **10**, **11** and **16** (Scheme 2), with only IR and ^{1}H NMR data (see, for instance, Scheme 6 [39]); it is possible that the double bond in structures of **11** class was ill-placed and that all the structures are of type **10**; structures **11** and **16** correspond to structure **23** in Scheme 3.

The results of Table 3 indicate that with the exception of the **a** series where both isomers have the same energy due to the weak perturbation of the methyl group, in the **b** and **c** series, tautomer **11** is clearly the most stable. However, this does not exclude the structure **10** as a kinetic product in neutral media (see the preceding section).

2.2.1.2. Origin of hydrazones. The hydrazones are obtained from the hemiaminals (or carbinolamines) **5** in an acid-catalyzed process (Scheme 7). The stereochemistry of the C=N double bond results from an *antiperiplanar* process [40–42] that is independent of the configuration of the central carbon atom (in Scheme 7 we have represented the **b** isomers with the *R* configuration) and only depends of the conformation about the N–C bond.

Isomers **A** and **B** correspond to the rotation about the N–C single bond with a low barrier; consequently, the geometry optimization led to only one structure that corresponds to **5b_A**. Protonation on the OH group resulted in a spontaneous water elimination; the stereochemistry of the C=N double bond corresponds an *antiperiplanar* process [40–42]. Finally, deprotonation affords phenylhydrazone **7b** of *E* configuration (Scheme 8).

The *E*/*Z* isomerism of the C=N double bond (in principle, the C=C double bond is *E* like in the starting chalcone) of hydrazones **6** and

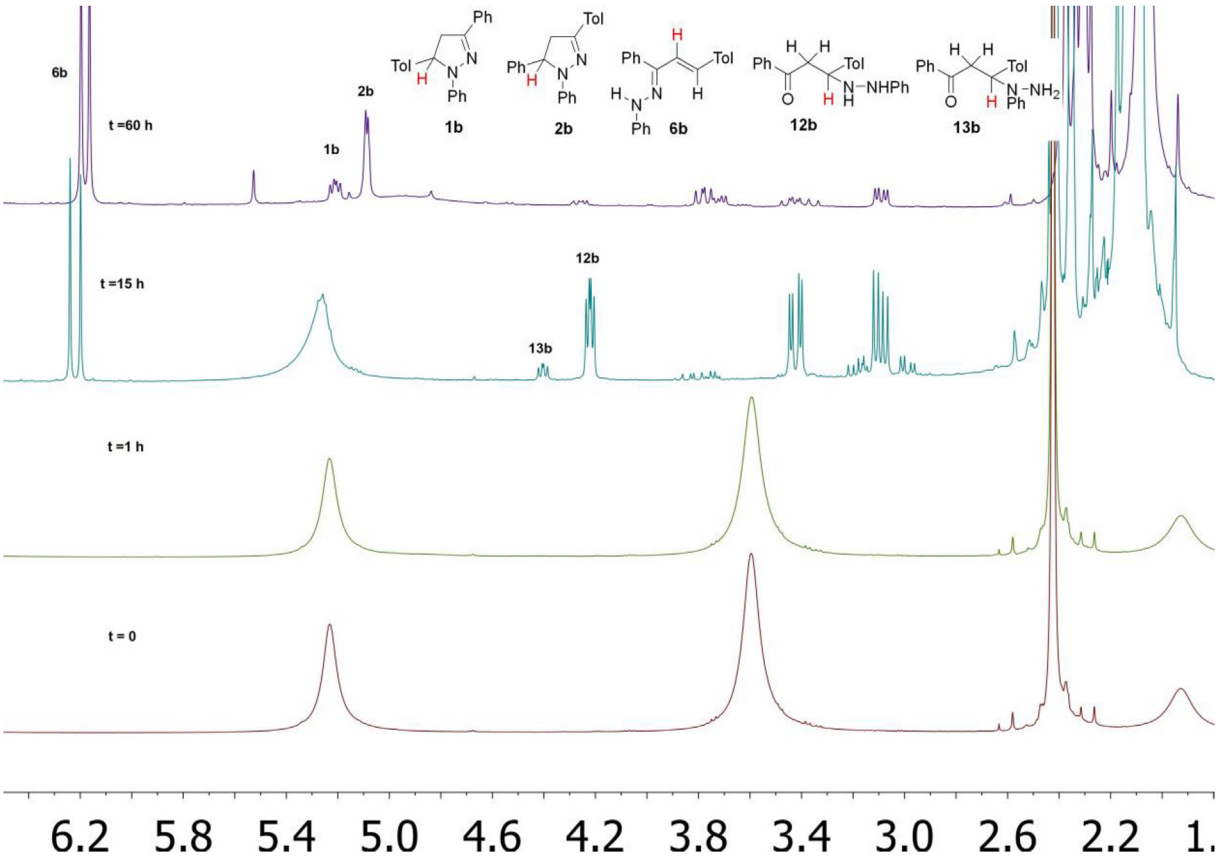


Fig. 3. Reaction of **3** with phenylhydrazine **4b** in the NMR tube. Solvent $CDCl_3$; AcOH (Cat). In red, protons pointed out in the spectrum.

7 is a problem relevant for the present work (Scheme 2). We have selected the *N*-phenyl derivatives **b**, the most studied, and considered the neutral molecules, and the two possible cations, protonated on N2 (**bH**$^+$) and protonated on N1 (**b'H**$^+$). The results of Table 3 allow eliminating the second kind of cations.

2.2.1.3. Syn/anti isomerism of hydrazones. The *E/Z* isomerism of hydrazones can occur by three mechanisms: i) by reversibility, liberating the chalcone and the hydrazine; this property is the basis of Lehn's dynamic libraries [43,44]; b) by inversion in-plane of the C═N bond, and c) by rotation out-of-plane about the C═N bond. In neutral hydrazones the *E/Z* isomerization takes place by inversion [45]; protonation on N2 prevents the inversion resulting in that only the rotation is allowed. We have represented in Fig. 7 two views of the three transition states (TSs). The IRCs of these processes (see the Supplementary data) indicate that the TS is directly linked to both minima of Fig. 7.

Like in other hydrazones, the TS between **6b** and **7b** corresponds to an inversion process; the protonation on N2 preventing the inversion take place by rotation. It appears that the protonation on N1 also take place by rotation.

The results of Table 4 show that protonation on N2 decreases considerably the barrier (the double bond character of the C═N bond decreases) but it is high enough for observe both isomers by NMR in any proportion (107.5 kJ mol^{-1} is too high for a rapid equilibration).

Dimmock et al. [26] reported a result very relevant for the present publication; when they prepare the thiosemicarbazone of the parent chalcone (phenyl instead of *p*-tolyl) they obtain at 0 time (approximately) 81% of the *E* isomer **7c"** and 19% of the *Z* isomer **6c"**, after 30 min (1800 s) the equilibrium is attained with 29% of **7c"** and 71% of **6c"**. Since they work at 37 °C (T = ~310 K) and $k = 1/900$ s^{-1}, $\Delta G^{\ddagger}_T$ = 19.12 * T (10.32 + log T/k) = 95.2 kJ mol^{-1}. Therefore, the kinetic product is the *E* isomer **7c"** and the thermodynamic is **6c"**. The results of Table 5 prove that the E/Z isomerization is acid-catalyzed with a calculated barrier of 97.2 kJ mol^{-1} very close to measured one, 95.2 kJ mol^{-1}.

The results of Table 5 prove that the E/Z isomerization is acid-catalyzed with a calculated barrier of 97.2 kJ mol^{-1} very close to measured one, 95.2 kJ mol^{-1}.

We have represented in Fig. 8 the five transition states we have calculated.

In acid medium we have observed at t = 48 h, two very small signals of similar intensity at 6.27 and 6.68 ppm (^3J = 15.7 Hz) that

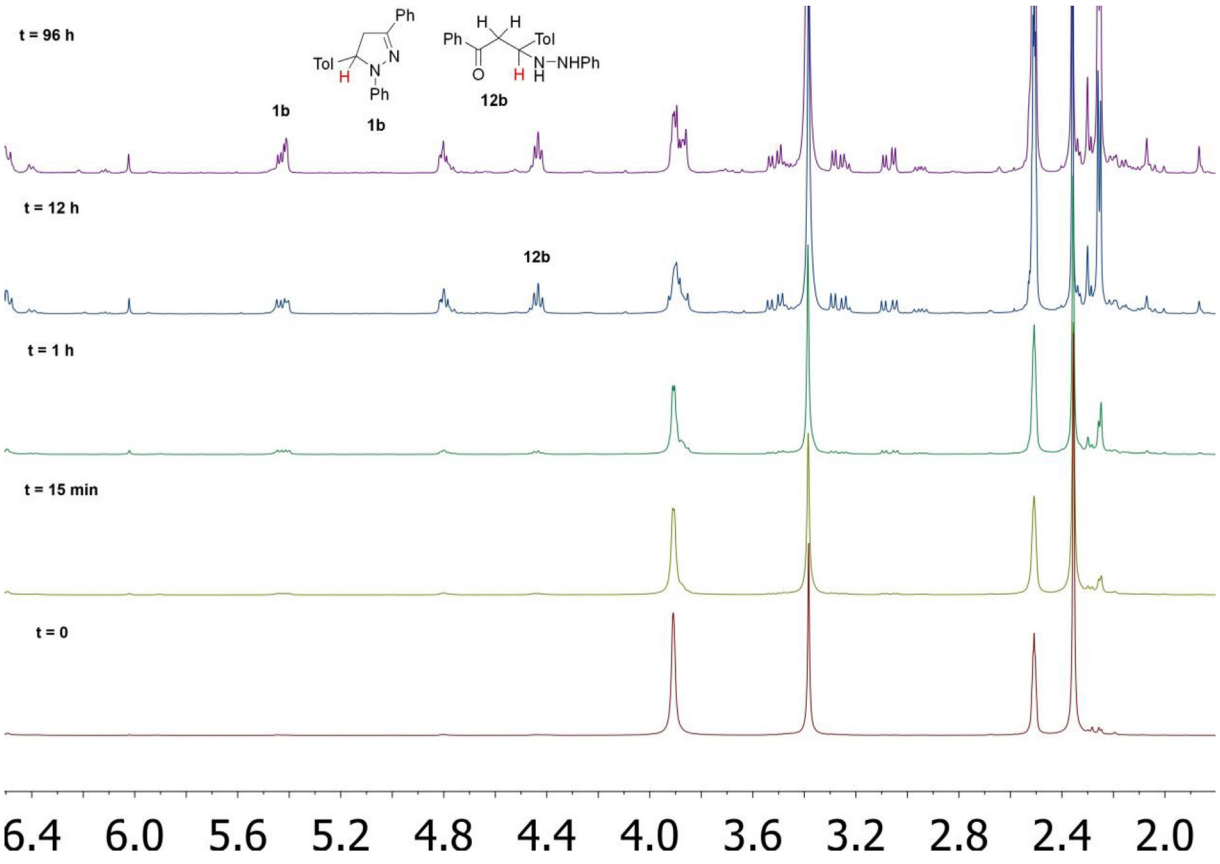


Fig. 4. Reaction of **3** with phenylhydrazine **4b** in the NMR tube. Solvent DMSO-d_6; with KOH. In red, protons pointed out in the spectrum.

correlate with signals at 6.96 and 7.46 ppm, respectively (Fig. 9). They correspond to the equilibrium mixture.

Advancing the section of NMR of hydrazones "2.2.2.1″, in Table 6 we reported the chemical shifts of semicarbazones.

We have prepared, isolated and recorded the NMR spectra of semicarbazones **6c** and **7c** because the data of Fig. 9 resulted from an experiment carried out in $CDCl_3$ containing AcOH, *i.e*. the semicarbazones are partly protonated. Since the *Z* isomer is more abundant than the *E* isomer, this indicates that the mixture has been evolved towards equilibrium. The assignment of the ^{1}H signals of the olefin, H4 and H5, has been carried out using a NOESY experiment (Fig. 10) that also allows to determine the *E/Z* configuration of the C═N bond.

2.2.1.4. Mechanism of cyclization of hydrazones into pyrazolines. The results of Table 7 show that the pyrazolines are much more stable than the hydrazones in the **a** and **b** series but only slightly more stable in the **c** series.

The mechanism of cyclization for neutral and N2-protonated hydrazones is represented in Scheme 9. In the case of neutral hydrazone, electrocyclization leads to a zwitterion **16'** [12,17].

The results reported in Table 8 shows that there is a considerable barrier between **7a** and **16a**′ and that the zwitterion lies well above the hydrazone. Once **16a**′ is reached an *N*-to-*N* proton transfer, very probably with a very low barrier assisted by the solvent or by protonation-deprotonation, led to the 3-pyrazoline **16a**, slightly less stable than **7a**. The final step **16a** → **1a** is similar to the transformation of **25** to **26** via **27** (Table 2 and Scheme 4). The TS of Table 7 corresponds to an elemental process as verified by IRC calculations (see Supplementary data).

2.2.2. NMR chemical shifts

We have reported in the supplementary data the ^{1}H and ^{13}C chemical shifts (Tables S1 and S2 respectively) as well as some ^{1}H–^{1}H SSCC. Unfortunately, most authors assign the ^{1}H of the olefin, the methyl group and the NHs but not the aromatic protons. Even worse is the part concerning the ^{13}C chemical shifts where usually a list of chemical shifts is given without neither reporting identical chemical shifts nor differentiating Cs from CHs. In Tables S1 and S2 we have tentatively assigned some of the literature signals and pointing out some anomalies.

2.2.2.1. Pyrazolines. Table S1 contain all the information available for the 2-pyrazolines discussed in this work, data from two papers

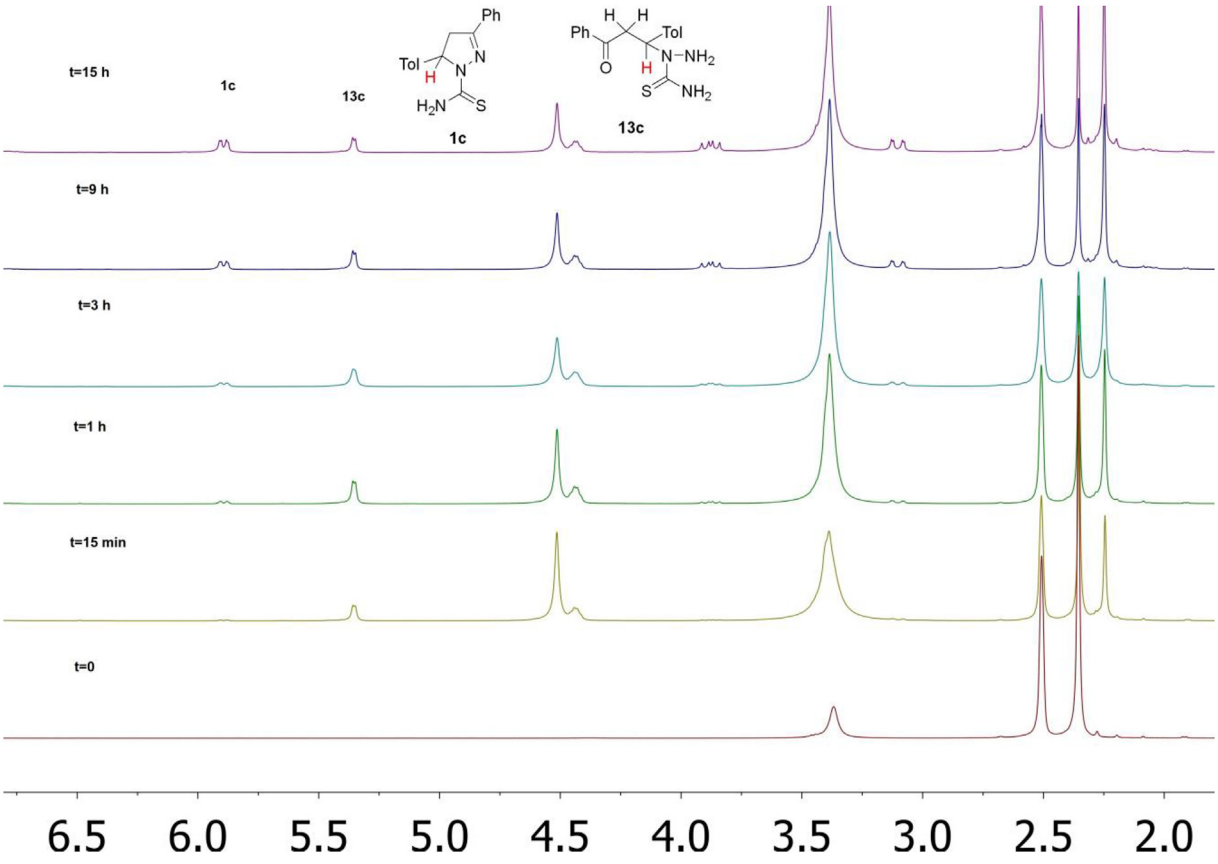
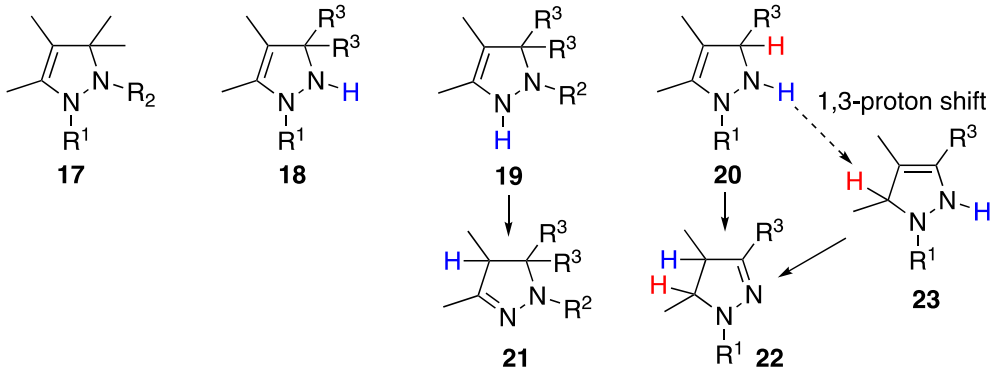


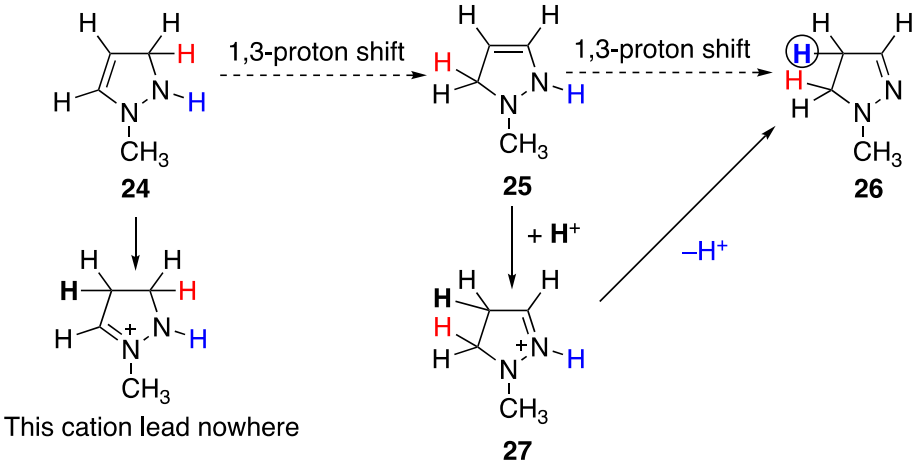
Fig. 5. Reaction of **3** with thiosemicarbazide **4c** in the NMR tube. Solvent DMSO-d_6; with KOH. In red, protons pointed out in the spectrum.



Scheme 3. The 3- to 2-pyrazolines isomerization channels.

not cited in the main text have been reported [46,47].

2.2.2.2. Hydrazones. The case of hydrazones, Table S2, is more complex; two references have been added where chemical shifts were reported [48,49]. We have added data of 2,4-dinitrophenylhydrazone of methylchalcone **6b** [48] because the data were assigned; in what concerns **6b** there are valuable ^{1}H NMR data but there was a problem [24a] with the coupling constant of the olefin (H_4 and H_5) part. In the Supplementary data of this publication several phenylhydrazones of chalcones were reported: chalcone itself ($^3J_{HH}$ = 16.4 Hz), 4-chlorochalcone ($^3J_{HH}$ = 17.0 Hz), 4-bromochalcone ($^3J_{HH}$ = 17.0 Hz), 4-nitrochalcone ($^3J_{HH}$ = 16.4 Hz) and 4-methoxychalcone ($^3J_{HH}$ = 17.1 Hz), however for 4-methylchalcone (our **6b**) they give twice $^3J_{HH}$ = 12.3 Hz). We think that there is no reason why this chalcone will be different and we have assumed that the 12.3 Hz value was an error.



Scheme 4. Isomerization of 3-pyrazolines into 2-pyrazolines (model compounds).

Table 2
Energetics (in kJ·mol^{-1}) of the tautomerization between the 3- and 2-pyrazolines of Scheme 5. Between brackets values from the starting materials.

24	TS (**24**→**int24**)	**int24**
60.8	355.1 [294.3]	279.0 [218.2]
TS (**int24**→**25**)	**25**	TS (**25**→**int25**)
372.0 [311.2]	63.1 [2.3]	313.8 [253.0]
int25	TS (**int25**→**26**)	**26**
292.5 [231.7]	330.4 [269.6]	0.0
10a	TS (**10a**→**int10a**)	**int10a**
57.7	358.9 [301.2]	236.0 [178.3]
TS (**int10a**→**11a**)	**11a**	TS (**11a**→**int11a**)
343.2 [285.5]	57.1 [−0.6]	341.2 [283.5]
int11a	TS (**int11a**→**2a**)	**2a**
332.9 [275.2]	346.3 [288.6]	0.0

There are other obvious errors, for instance the coupling constants of **6c** or **7c** [27] cannot be 8.0 or 8.1 Hz but probably 16.0 or 16.2 Hz.

2.2.2.3. Comparison experimental vs. calculated chemical shifts. We have calculated much more chemical shifts than there are experimental values (Tables S1 and S2) but they could be useful to use them as predicted values (Table S3). The ^{1}H chemical shifts of the NH protons cannot be used since they are very sensitive to solvent effects.

^{1}H: (0.21 ± 0.06) + (0.97 ± 0.01) Calc., n = 82, R^2 = 0.992, RMS error = 0.18 ppm (1)

^{13}C: (1.001 ± 0.002) Calc. + (6.8 ± 1.5) C3 hydrazones, n = 112, R^2 = 1.000, RMS error = 2.6 ppm (2)

^{1}H & ^{13}C: (1.000 ± 0.001) Calc. + (6.9 ± 0.9) C3 hydrazones, n = 194, R^2 = 0.9997, RMS error = 1.55 ppm (3)

The ^{1}H chemical shifts are the less well explained by the calculations (see Eq. (1)) because of their smaller range of ppm values and because the more sensitivity to solvent effects, particularly hydrogen bonds. Nevertheless, the square correlation coefficient and the root-mean-square error are acceptable.

The signal of the C3 carbon of hydrazones, i. e. the C=N, deviates systematically (Eq. (2)). The deviation has been calculated adding a variable = 1 for these carbons and = 0 for all the others. The effect is important, 6.8 ppm, and the deviation small (1.5 ppm) for a phenomenon that remains unexplained.

In Eq. (3) ^{1}H and ^{13}C chemical shifts were treated together with very satisfying results.

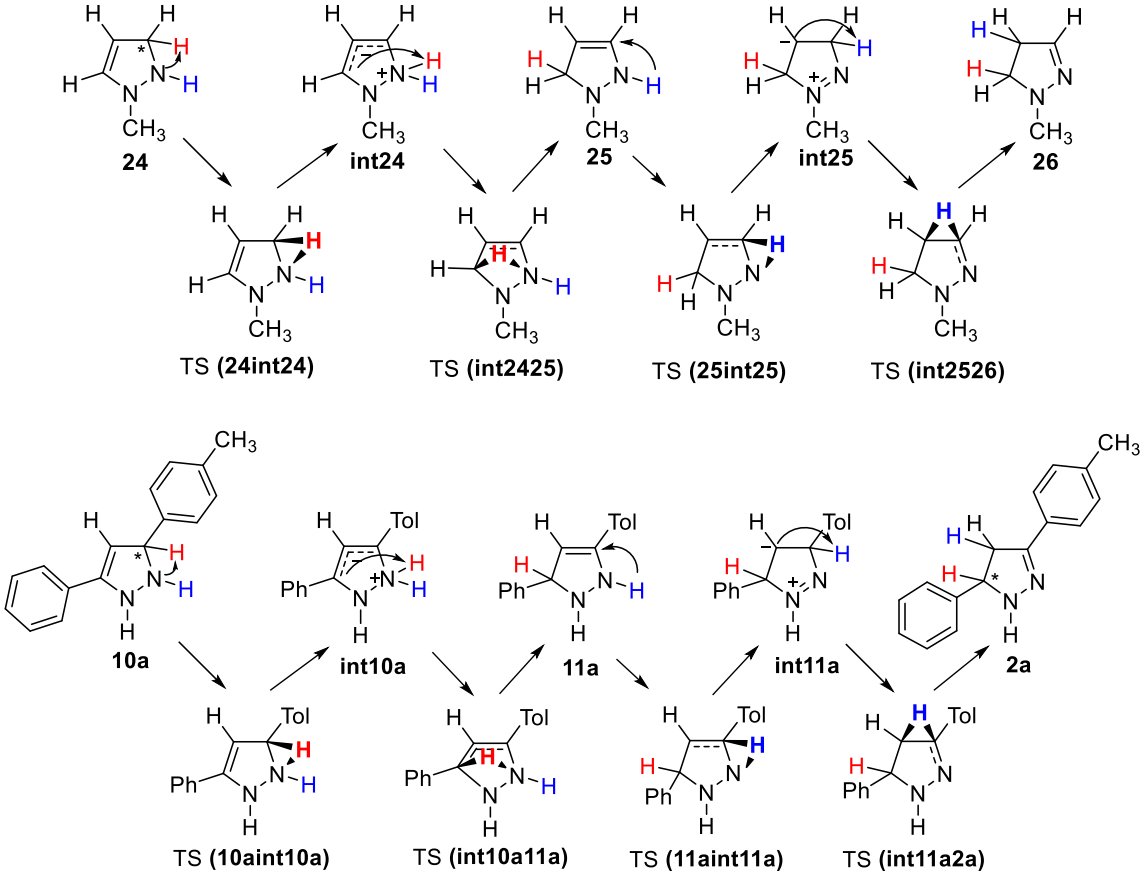
3. Conclusions

We have summarized the results from the literature (in blue) and our results (in red) in Scheme 8. With regard to the possibilities of Scheme 2, Scheme 10 has confirmed and rejected some ways, this being the main conclusion of the present paper, where not only the mechanism of formation of 2-pyrazolines but also the *syn/anti* isomerism of hydrazones was studied.

Besides a series of experiments where mixtures of the reagents, methylchalcone and three hydrazines, were followed in the NMR tube within time, we have used X-ray structures from the CSD and prepared some hydrazones and 2-pyrazolines to record and assign their ^{1}H and ^{13}C NMR spectra using bidimensional techniques.

Theoretical calculations at the B3LYP/6−311++G (d,p) provided energies both of the minima and transition states; the optimized geometries of the minima were used to calculated absolute shieldings by means of the GIAO approximation. An examination of the TS shows how acid-catalysis decreases significantly the barriers.

The use of IRC calculations has proved that in most cases the TSs are directly linked to the minima but in one case (Scheme 4) two intermediates have been characterized; although this has not practical consequences, they lay very high in energy, it



Scheme 5. The five-step mechanism of isomerization of 3- to 2-pyrazolines.

demonstrated the necessity of this type of calculations for ascertain new reaction mechanisms.

4. Experimental section

4.1. 3-p-Methylphenyl-1-phenylpropenone (*3*)

To a solution of 4-methylbenzaldehyde (1.2 g, 10 mmol) and acetophenone (1.2 g, 10 mmol) in ethanol (5 mL) a solution of NaOH (200 mg) in ethanol (5 mL) was added dropwise. The suspension was stirred for 1 h and the solid was filtered to give 1.8 g (81%) of pure **3** (m.p. 93-95 °C).

^{1}H NMR ($CDCl_3$): 8.04 (dd, J = 8.1, 1.5, 2H), 7.83, (d, J = 15.6 Hz, 1H), 7.61 (tt, J = 7.2, 1.3, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H), 7.53 (t, J = 7.5 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 2.42 (s, 3H).

4.2. 3-Phenyl-5-p-tolyl-4,5-dihydro-1H-pyrazole (*1a*)

A solution of 3-*p*-methylphenyl-1-phenylpropenone (**3**) (33.4 mg, 0.15 mmol), hydrazine hydrate (**4a**) (0,6 mmol) in chloroform-d_6 (0.6 mL) was maintained at 25 °C and followed by NMR. When the starting material has disappeared (48 h aprox.) chloroform (5 mL) was added, water was removed, and the organic solution dried over anhydrous magnesium sulfate 32 mg (91%) of **1a**. (m.p. 106-108 °C).

^{1}H NMR (DMSO-d_6): δ 7.63 (d, J = 6.9 Hz, 2H), 7.38 (t, J = 7.1 Hz, 2H), 7.31 (t, J = 7.1 Hz, 1H), 7.17 (d, J = 7.6 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 4.80 (t, J = 10.3 Hz, 1H), 3.43 (bs, 2H), 3.42 (dd, J = 16.2, 10.4 Hz, 1H), 2.82 (dd, J = 16.3, 10.7 Hz, 1H). 2.25 (s, 3H).

^{13}C NMR (DMSO-d_6): δ 149.13, 140.42, 136.66, 133.77, 129.55, 129.40, 128.96, 126.99, 125.86, 63.83, 41.00, 21.15.

^{1}H NMR ($CDCl_3$): δ 7,66 (d, J = 7.9 Hz, 2H), 7.37 (t, J = 7.0 Hz, 2H), 7.33 (t, J = 6.9 Hz, 1H), 7.24 (d, J = 7.5 Hz, 2H), 7.14 (d, J = 7.5 Hz, 2H), 5.98 (s, 1H), 4.88 (t, J = 9.5 Hz, 1H), 3.44 (dd, J = 16.2, 10.6 Hz, 1H), 3.03 (dd, J = 16.3, 8.7 Hz, 1H). 2.25 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 151.29, 169.87, 137.50, 132.92, 129.51, 128.76, 128.54, 126.26, 126.03, 64.06, 41.33, 21.11.

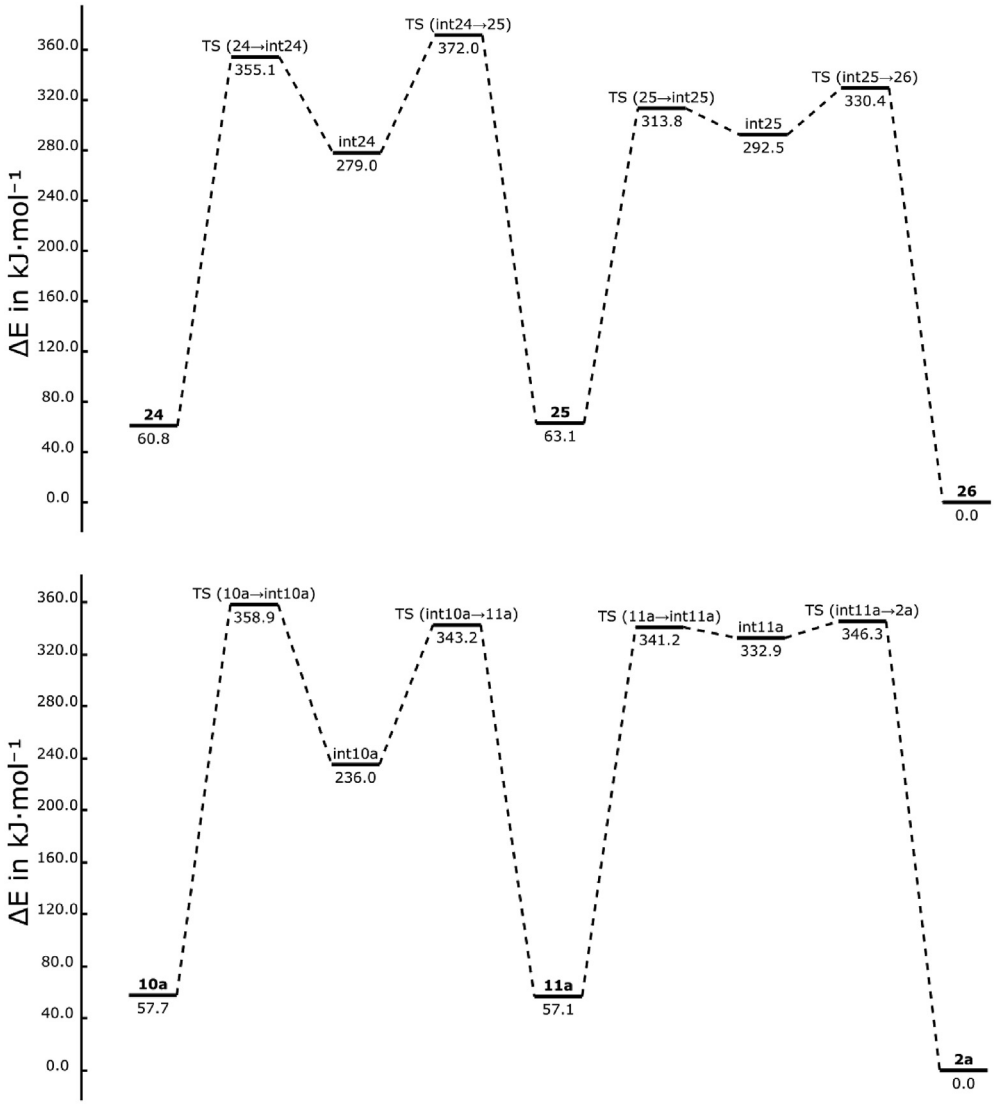
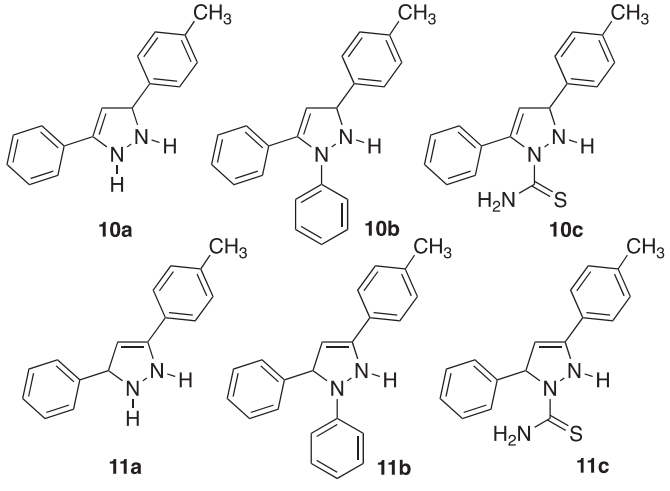


Fig. 6. Energetic profiles corresponding to the **24** → **25** → **26** and **10a** → **11a** → **2a** sequences.



Scheme 6. The position of the double bond in 3-pyrazolines.

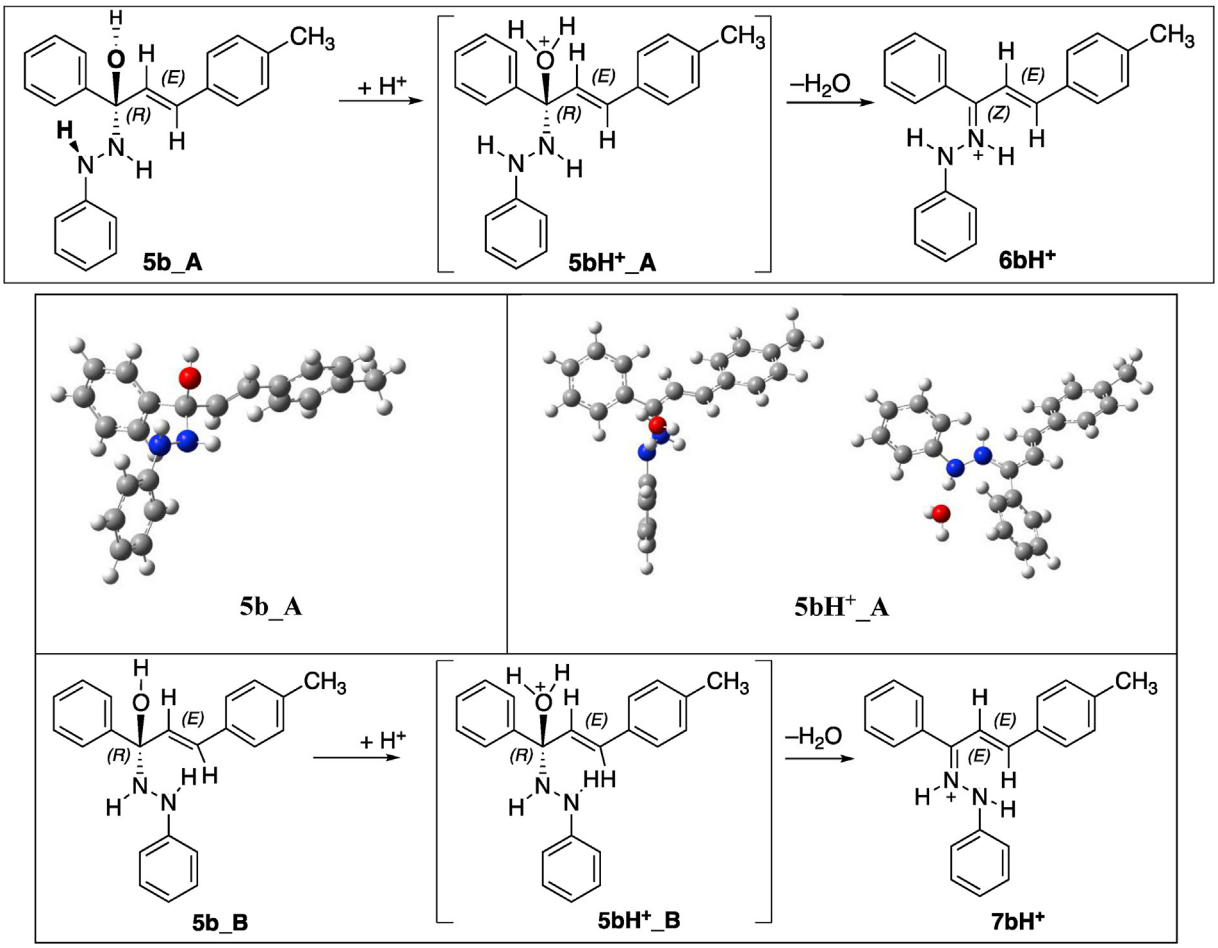
Table 3
Energetics (in kJ·mol^{-1}) of the tautomerism between 3-pyrazolines.

	a	b	c
10	0.6	14.6	35.8
11	0.0	0.0	0.0

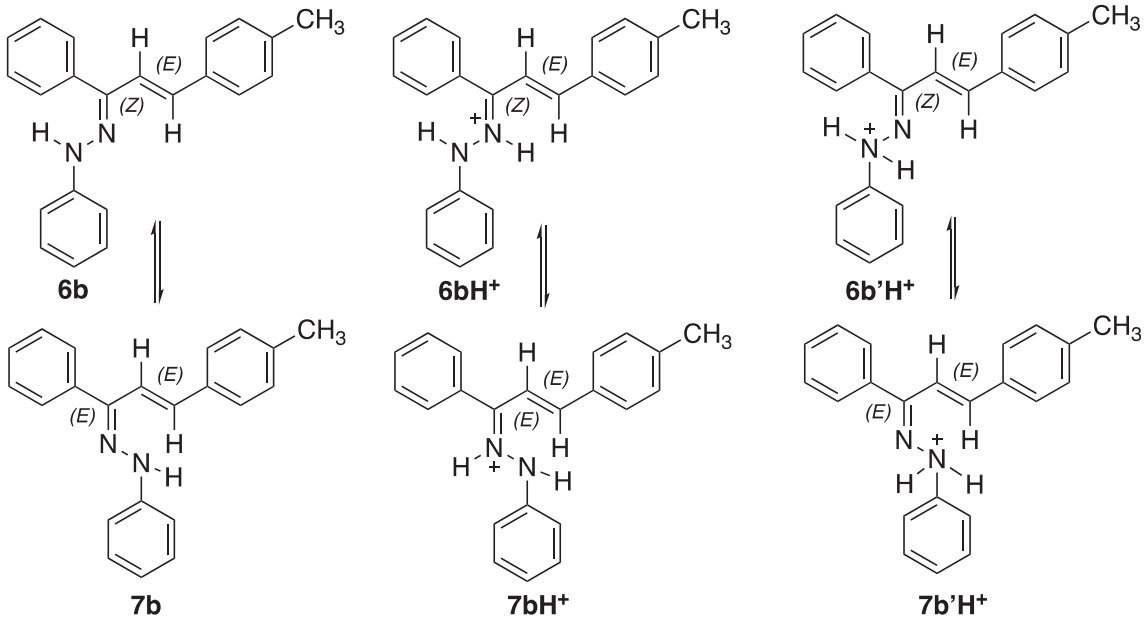
4.3. 1,3-Diphenyl-5-p-tolyl-4,5-dihydro-1H-pyrazole (***1b***)

A solution of 3-*p*-methylphenyl-1-phenylpropenone (**3**) (888 mg, 4 mmol), phenylhydrazine (**4b**) (432 mg, 4 mmol) and acetic acid (2 drops) in ethanol (10 mL) was heated to reflux for 15 h. A similar volume of water was added and the solid was filtered to give 800 mg (64%) of **1b** (m.p. 127-129 °C).

^{1}H NMR ($CDCl_3$): δ 7.72 (d, J = 7.1 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.31 (t, J = 6.9 Hz, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.17 (t, J = 7.6 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 7.6 Hz, 2H), 6.77 (t, J = 7.3, 1H), 5.24 (dd, J = 12.2, 7.2 Hz, 1H), 3.82 (dd, J = 12.4, 17.0, 1H) 3.12 (dd, J = 17.1, 7.1, 1H), 2.33 (s, 3H).



Scheme 7. The acid-catalyzed formation of hydrazones **6** and **7** (two views of **5bH$^+$_A**).



Scheme 8. The **6/7** isomerism of hydrazones and their protonated derivatives.

^{13}C NMR ($CDCl_3$): δ 146.70, 144.93, 139.67, 137.24, 132.84, 129.81, 128.89, 128.54, 125.82, 125.73, 119.04, 113.38, 64.31, 43.65, 21.12.

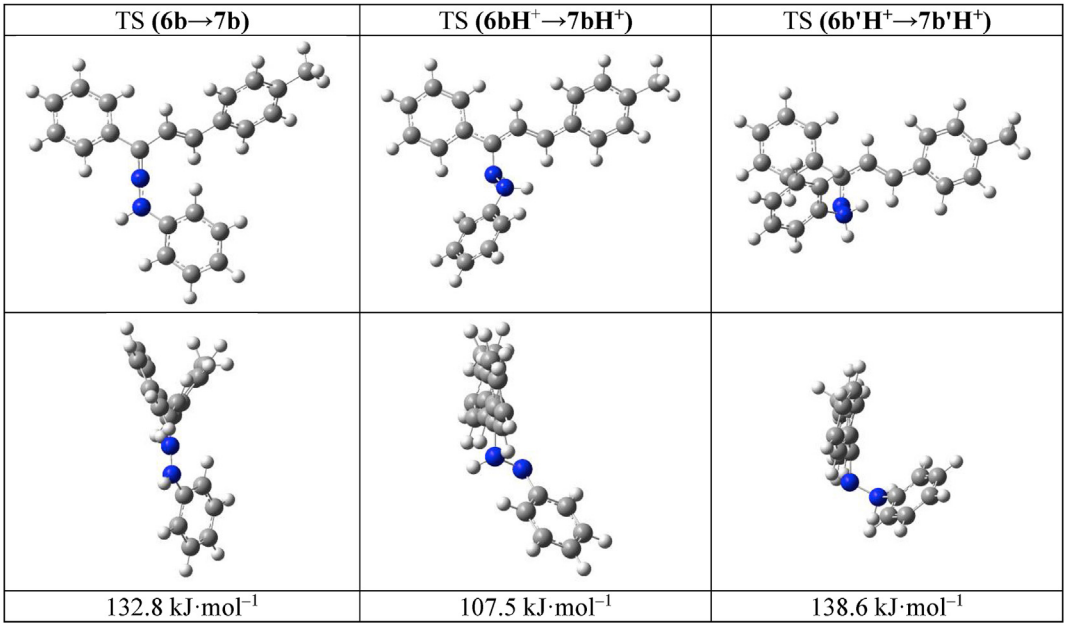


Fig. 7. The E/Z isomerization of neutral and protonated phenylhydrazones.

Table 4
Energetics (in kJ·mol^{-1}) of the *E/Z* isomerism of phenylhydrazones and their conjugated cations.

Neutral	**TS**	**6b**	**TS (6b→7b)**	**7b**	**6bH$^+$/6b′H$^+$**	**7b H$^+$/7b′H$^+$**
	inversion	0.0	132.8	0.1		
Cation, protonated on N2		**6bH$^+$**	TS (**6bH$^+$→7bH$^+$**)	**7bH$^+$**		
	rotation	0.0	107.5	−7.6	52.1	64.2
Cation, protonated on N1		**6b′H$^+$**	TS (**6b′H$^+$→7b′H$^+$**)	**7b′H$^+$**		
	rotation	0.0	138.6	4.5		

Table 5
Energetics (in kJ·mol^{-1}) of the *E/Z* isomerism of thiosemicarbazones and their conjugated cations.

Neutral	**TS**	**6c**	**TS (6c→7c)**	**7c**
	inversion	0.0	139.6	0.3
Cation, protonated on N2		**6cH$^+$**	TS (**6cH$^+$→7cH$^+$**)	**7cH$^+$**
	rotation	0.0	97.2	−22.7

*4.4. 3-Phenyl-5-p-tolyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**1c**)*

3-*p*-methylphenyl-1-phenylpropenone (**3**) (444 mg, 2 mmol), thiosemicarbazide (**4c**) (182 mg, 2 mmol) and KOH (112 mg, 2 mmol) in ethanol (10 mL) were heated to reflux for 4 h. The solution was cooled and the solid was filtered and identified as a mixture of **3** and **12c**. Water was added to the filtrate and the suspension was stirred for 1 h, the solid was filtered and purified by flash chromatography on silica gel (hexane: ethyl acetate 4 : 1) to give 390 mg (64%) of **1c** (m.p. 151-153 °C).

^{1}H NMR ($CDCl_3$): δ 7.73 (d, J = 7.8 Hz, 2H), 7.45 (t, J = 7.0 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6,23 (bs, 2H), 6.04 (dd, J = 11.7, 3.7 Hz, 1H), 3.84 (dd, J = 17.6, 11.5 Hz, 1H), 3.21 (dd, J = 17.6, 3.5 Hz, 1H), 2.31 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 176.72, 156.03, 138.90, 137.31, 131.03, 130.72, 129.60, 128.88, 126.97, 125.37, 63.30, 43.17, 21.17.

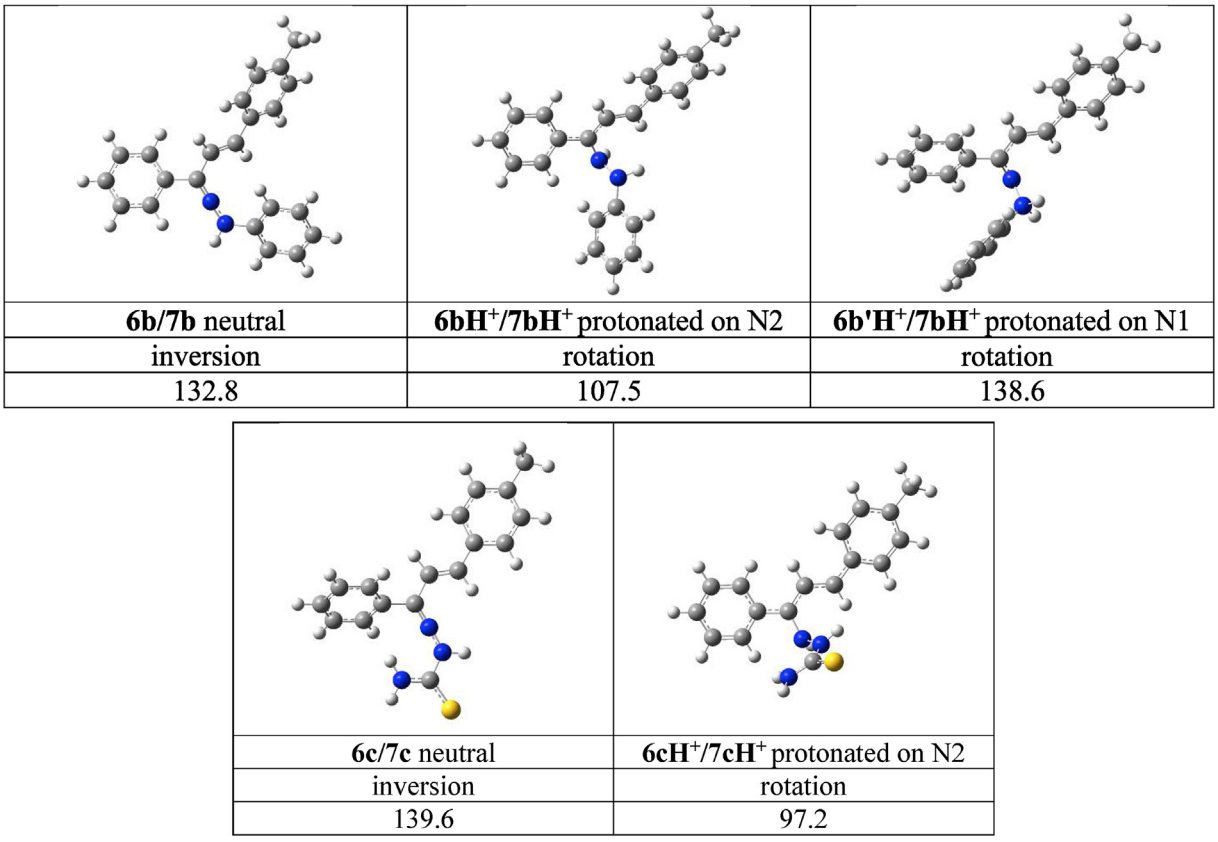


Fig. 8. The three TSs of phenylhydrazones and the two TSs of semicarbazones.

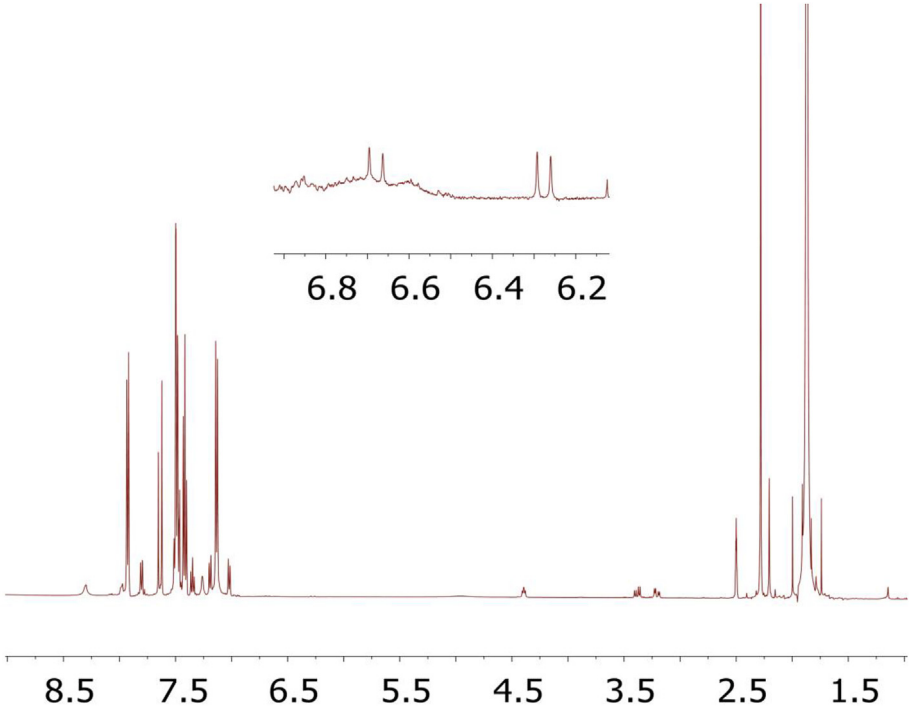


Fig. 9. The ^{1}H NMR spectrum of thiosemicarbazones **6c** and **7c** in $CDCl_3$ with AcOH (cat).

Table 6
^{1}H chemical shifts of the olefinic part of thiosemicarbazones.

Comp.	Calc.	(Ph/Ph)* A	This work (Fig. 9)	This work (isolated products)
		DMSO-d_6	AcOH + $CDCl_3$	$CDCl_3$
6c (*Z*)	6.70, H4	6.77, 71%	6.68, $^3J_{HH}$ = 15.6 Hz	6.40, H4, 65%, $^3J_{HH}$ = 16.2 Hz
	7.45, H5	–	7.46, $^3J_{HH}$ = 15.6 Hz	7.01, H5, 65%, $^3J_{HH}$ = 16.2 Hz
7c (*E*)	6.58, H4	6.45, 29%	6.27, $^3J_{HH}$ = 15.8 Hz	6.90, H4, 35%, $^3J_{HH}$ = 16.3 Hz
	7.15, H5	–	6.96 $^3J_{HH}$ = 15.8 Hz	6.95, H4, 35%, $^3J_{HH}$ = 16.3 Hz

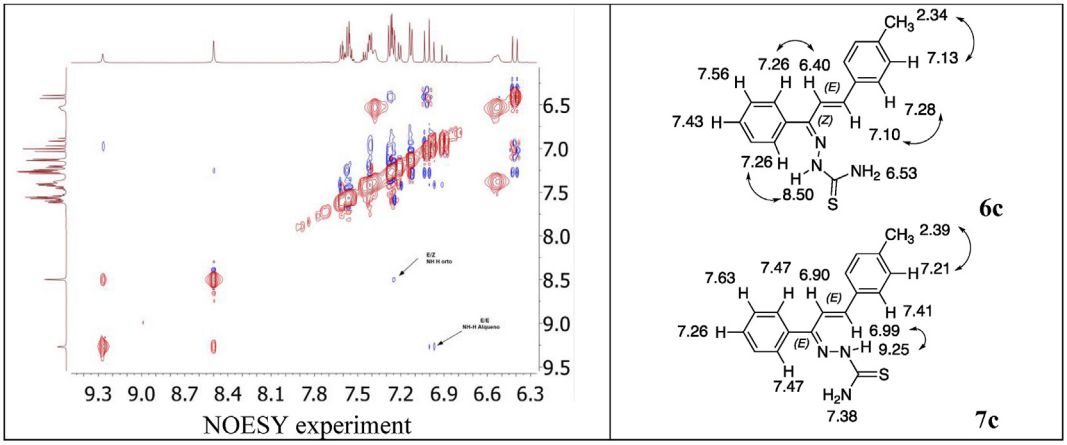
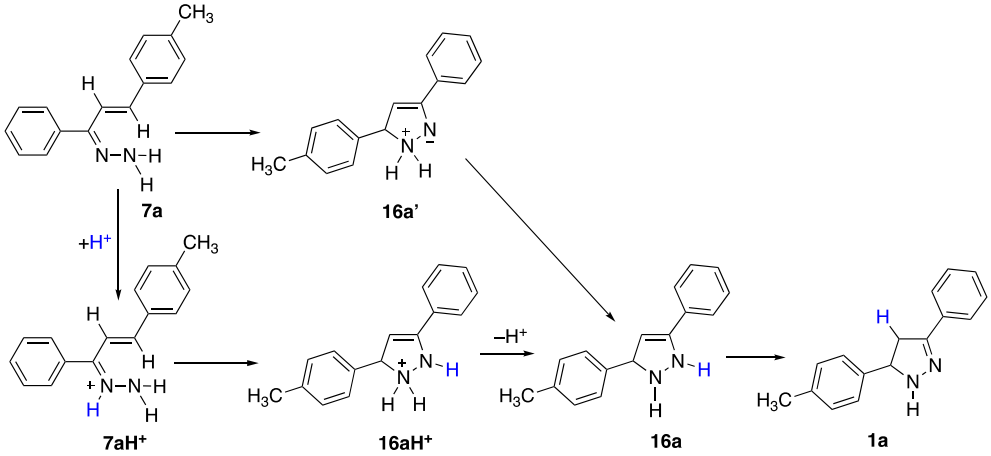


Fig. 10. The NOESY experiment of thiosemicarbazones **6c** and **7c** in $CDCl_3$.

Table 7
Energetics (in kJ·mol^{-1}) of the *E/Z* isomerism of hydrazones and their corresponding pyrazolines **1**.

	6	**7**	**1**
a series, R^1 = H	44.8	42.3	0.0
b series, R^1 = C_6H_5	38.3	38.1	0.0
c series, R^1 = $CSNH_2$	6.3	6.5	0.0



Scheme 9. The mechanisms of cyclization of hydrazones into 2-pyrazolines.

Table 8
Energetics (in kJ·mol^{-1}) and N–C distances (Å) of the cyclization of hydrazones into pyrazolines of Scheme 9.

Model	**7a**				TS (**7a**→**7aH**$^+$)	**16a′**	**16a**
	0.0	**6c**	**7c**	**6cH**$^+$	**7cH**$^+$	147.6	118.7	19.9
Scheme 2	**7aH**$^+$					TS (**7aH**$^+$→**16aH**$^+$)	**16aH**$^+$	
	0.0					93.6	61.0	
N–C (Å)						2.010	1.575	

4.5. 2-N-(3-oxo-3-phenyl-1-p-tolyl)thiosemicarbazide (**12c**)

^{1}H NMR (DMSO-d_6): δ 7.88 (d, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.3 Hz, 2H), 7.31 (d, 2H), 7.09 (d, J = 7.7 Hz, 2H), 5.33 (bd, 1H), 4.42 (dq, 1H), 4.41 (bs, 1H), 2.27 (s, 3H). Very impure, it contains a large amount of chalcone **3**.

4.6. (1Z)-1-((E)-1-phenyl-3-p-tolylallylidene)thiosemicarbazide (**6c**) and (1E)-1-((E)-1-phenyl-3-p-tolylallylidene) thiosemicarbazide (**7c**). Compound **6c** was reported in Ref. [27] but only its ^{1}H NMR data

A solution of 3-*p*-methylphenyl-1-phenylpropenone (**3**) (149 mg, 0.67 mmol), thiosemicarbazide (**4c**) (61 mg, 0.67 mmol) and acetic acid (335 μL) in ethanol (10 mL) were heated to reflux for 24 h. The solvent was removed *in vacuo* and the crude product was chromatographed on silica gel using hexane: ethyl acetate 4:1 as the eluent to give 82 mg (43%) of a 65%: 35% mixture of *Z/E* and *E/E* thiosemicarbazones that evolves to 86%: 14% within time.

(*1Z*)-1-((*E*)-1-phenyl-3-*p*-tolylallylidene)thiosemicarbazide **6c**.

^{1}H NMR ($CDCl_3$): δ 8.50 (bs, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.9 Hz, 2H), 1H) 7.25 (dd, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 16.2 Hz, 1H), 6.53 and 6.55 (bs, 2H), 6.41 (d, J = 16.2 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 178.39, 152.70, 139.32, 139.03, 133.09, 130.31, 129.99, 129.57, 128.34, 127.64, 128.85, 127.09, 21.39.

(*1E*)-1-((*E*)-1-phenyl-3-*p*-tolylallylidene)thiosemicarbazide **7c**.

^{1}H NMR ($CDCl_3$): δ 9.27 (bs, 1H), 7.38 (bs, 2H), 7.60 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.46–7.41 (m, 4H), 6.99 (d, J = 16.3 Hz, 1H), 6.90 (d, J = 16.3 Hz, 1H), 2.38 s (3H).

^{13}C NMR ($CDCl_3$): δ 179.04, 150.53, 142.73, 140.51, 136.49, 132.13, 130.09, 129.76, 128.99, 128.48, 127.63, 115.20, 21.49.

5. NMR experiments

NMR experiments were recorded in Bruker Avance Neo instruments working at 500.16 and 399.77 MHz for ^{1}H and at 125.76 and 100.52 MHz for ^{13}C using the standard Bruker pulse sequences for ^{1}H, ^{13}C, COSY, NOESY and HSQC experiments. Typically, 16 transits and a 30-degree flip angle was used for ^{1}H, 1024 transits and a 90-degree flip angle was used for ^{13}C. For 2D experiments the following parameters were used: 1 transit and 128 increments for COSY, and 4 transits and 256 increments for NOESY and HSQC.

6. Computational details

All the calculations have been carried out using the Gaussian-16 package [50]. In all cases, we have used the B3LYP/6–311++G (d,p) method [51]; frequency calculations were carried out to verify that the structures obtained correspond to energetic minima (I = 0) or to transition states (TS, I = 1). These geometries have been used for the calculation of the absolute chemical shieldings with the GIAO method [52,53].

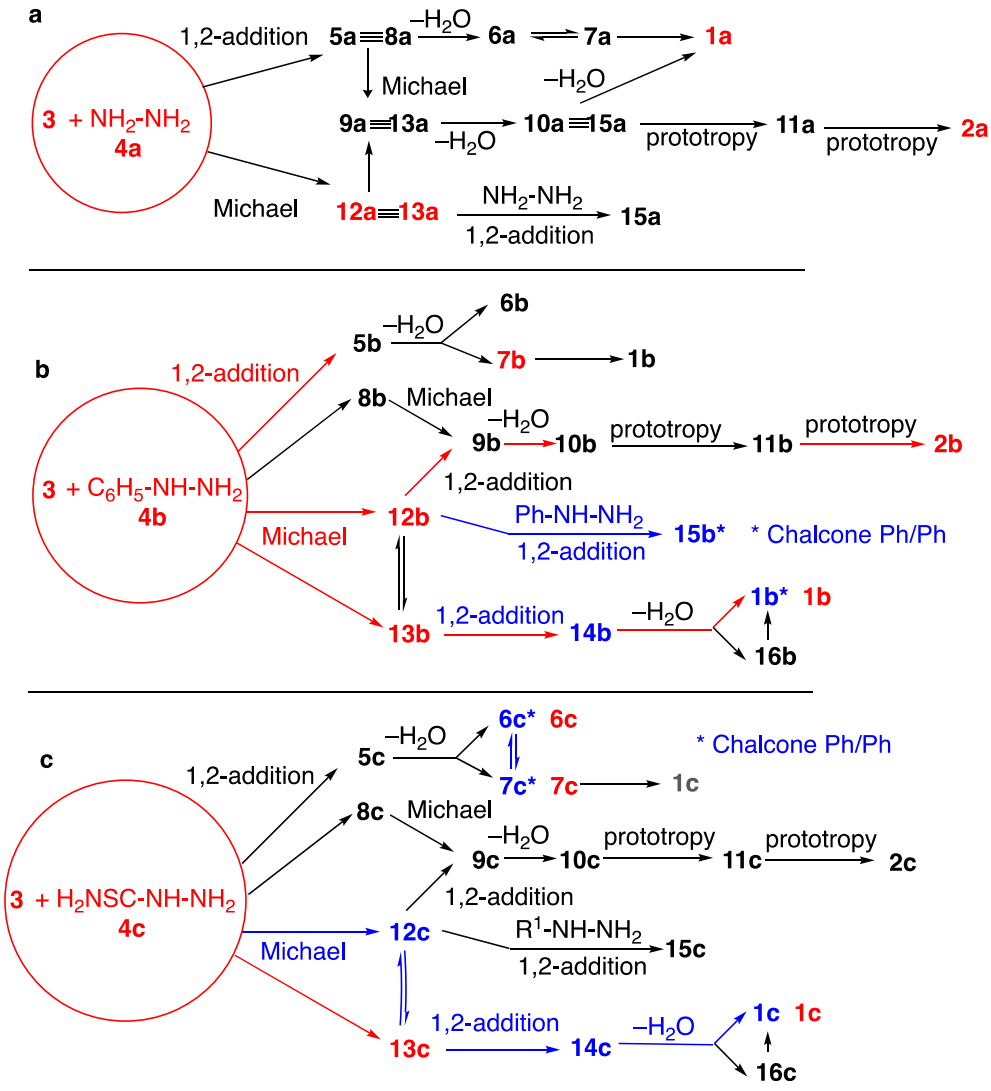
Equations 4-6 have been used to transform absolute shieldings into chemical shifts:

δ^1H = 31.0–0.97 x σ^1H, (reference TMS, 0.00 ppm) (Eq. (4)) [54]

δ^{13}C = 175.7–0.963 x σ^{13}C, (reference TMS, 0.00 ppm) (Eq. (5)) [55]

δ^{15}N = −152.0–0.946 x σ^{15}N, (reference TMS, 0.00 ppm) (Eq. (6)) [55].

In order to locate the intermediates at either sites of the TS point we followed the vibrational mode of the imaginary frequency – forward and backward – along the intrinsic reaction coordinate (IRC) [56,57] and relaxed the geometry for searching an energy (local) minimum.



Scheme 10. The possible (in black) and observed processes (in red our results; in blue literature results) for the three hydrazines. The **c** series correspond to experiments carried out in basic media. The intermediates have not been represented.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132413.

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