The reaction between hydrazines and β-dicarbonyl compounds: proposal for a mechanism

Shiv P. Singh, Dalip Kumar, Hitesh Batra, Rajesh Naithani, Isabel Rozas, and José Elguero

Abstract: The reaction between aryl or heteroarylhydrazines with fluorinated β-diketones (CF_3COCH_2COR) yields a variety of 3-, 5-, and 3,5-trifluoromethylpyrazoles and 5-trifluoromethyl-5-hydroxy-Δ^2-pyrazolines. Twenty-one of such compounds have been isolated and identified by ^{13}C and ^{19}F NMR. Together with the results from the literature they provide a comprehensive overview of the reaction. Semi-empirical calculations at the PM3 level have been used to rationalize these results. The outcome that emerges seems to be that the dehydration of a pair of 3,5-dihydroxypyrazolidines kinetically controls the isomer formed.

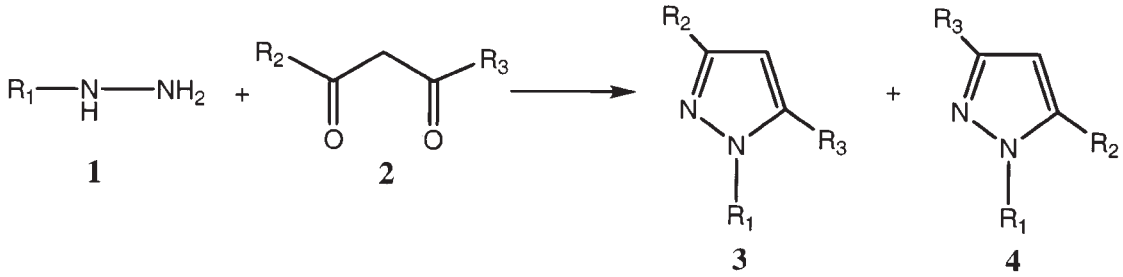
Key words: hydrazines, 1,3-diketones, pyrazolines, pyrazoles, PM3 calculations.

Résumé : La réaction entre des aryl ou hétéroarylhydrazines et des β-dicétones fluorées (CF_3COCH_2COR) donne lieu a une série des 3-, 5- et 3,5-trifluorométhylpyrazoles et 5-trifluorométhyl-5-hydroxy-Δ^2-pyrazolines. Vingt-et-un de ces composés ont été isolés et caractérisés par RMN du ^{13}C et ^{19}F. Avec l'addition des résultats de la littérature, ils donnent une image cohérente de la réaction. Des calculs semi-empiriques PM3 ont été utilisés pour expliquer ces résultats. L'image qui apparaît est celle d'une réaction cinétiquement contrôlée qui correspond à la déshydratation d'une paire de 3,5-dihydroxy-pyrazolidines en équilibre.

Mots clés : hydrazines, 1,3-dicétones, pyrazolines, pyrazoles, calculs PM3.

Introduction

The reaction between a monosubstituted hydrazine (**1**) and a nonsymmetrical β-diketone (**2**) always leads to the formation of a mixture of pyrazole isomers (**3** and **4**) even when one of them is present in a very small amount and the process can be considered regioselective.



This apparently simple reaction, which constitutes the main synthetic approach to pyrazoles (1–5), conceals a complex mechanistic problem. We have summarized in Scheme 1 the different routes that can lead to the two actually isolated compounds making clear where the difficulty of the problem lies. Considering that hydrazine can react initially by the NH (D) or the NH_2 (E) and that a β-diketone has three tautomeric forms (**A**, **B**, and **C**) with two reactive centers, each isomer can be formed by six different routes.

In some cases, it has been possible to isolate the 5-hydroxy-Δ^2-pyrazoline intermediates (**7**) (Scheme 2), but this does not help to solve the mechanistic riddle: which are the route or routes operative in Scheme 1? From low-temperature NMR experiments and from qualitative results, the mechanism represented in Scheme 2 is generally accepted for the synthesis of pyrazoles. The key intermediate is the 3,5-dihydroxypyrazolidine **5** and the formation of both N—C bonds (N2—C3 and N1—C5) of the carbinolamine groups are considered reversible, i.e., when R_2 and R_3 are different, both dihydroxypyrazolidines **5′** and **5″** should be in equilibrium.

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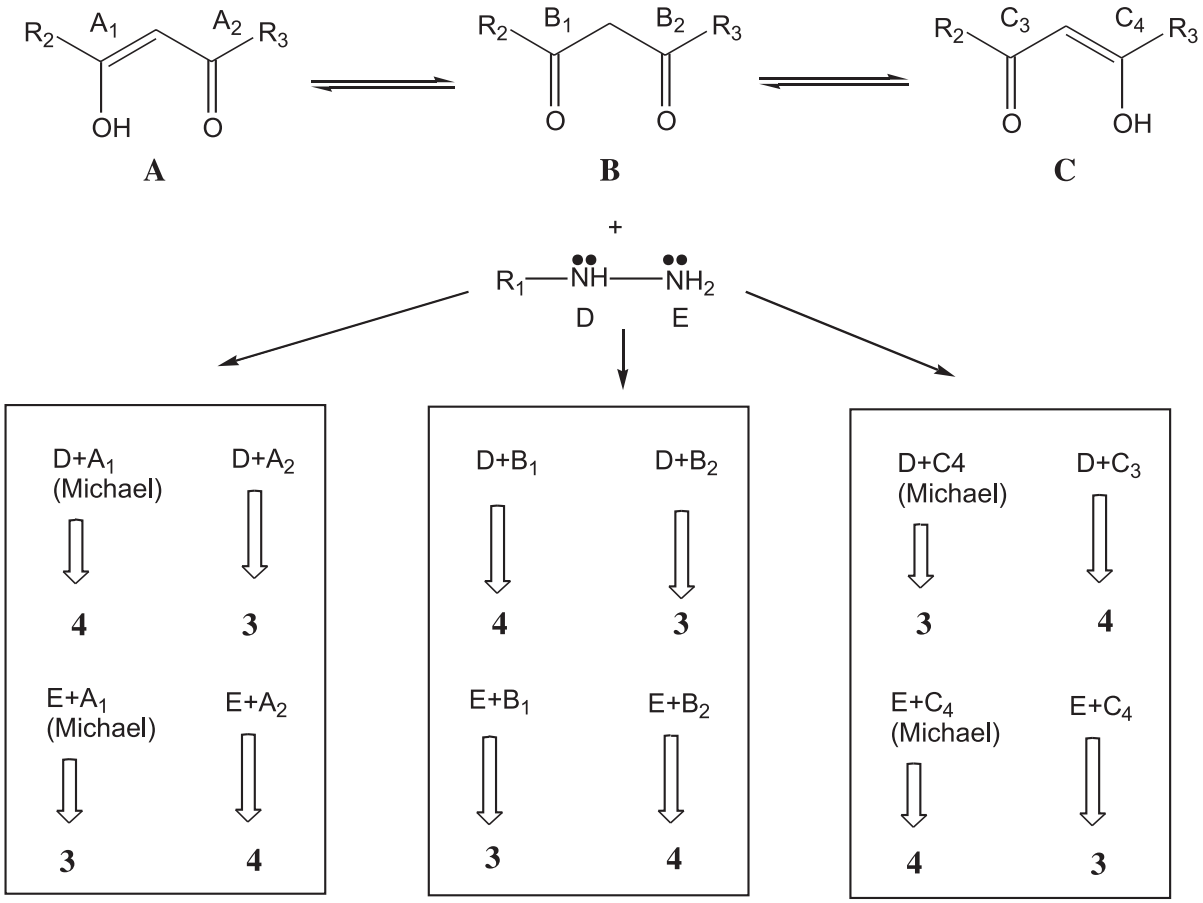
Scheme 1.



Scheme 2.

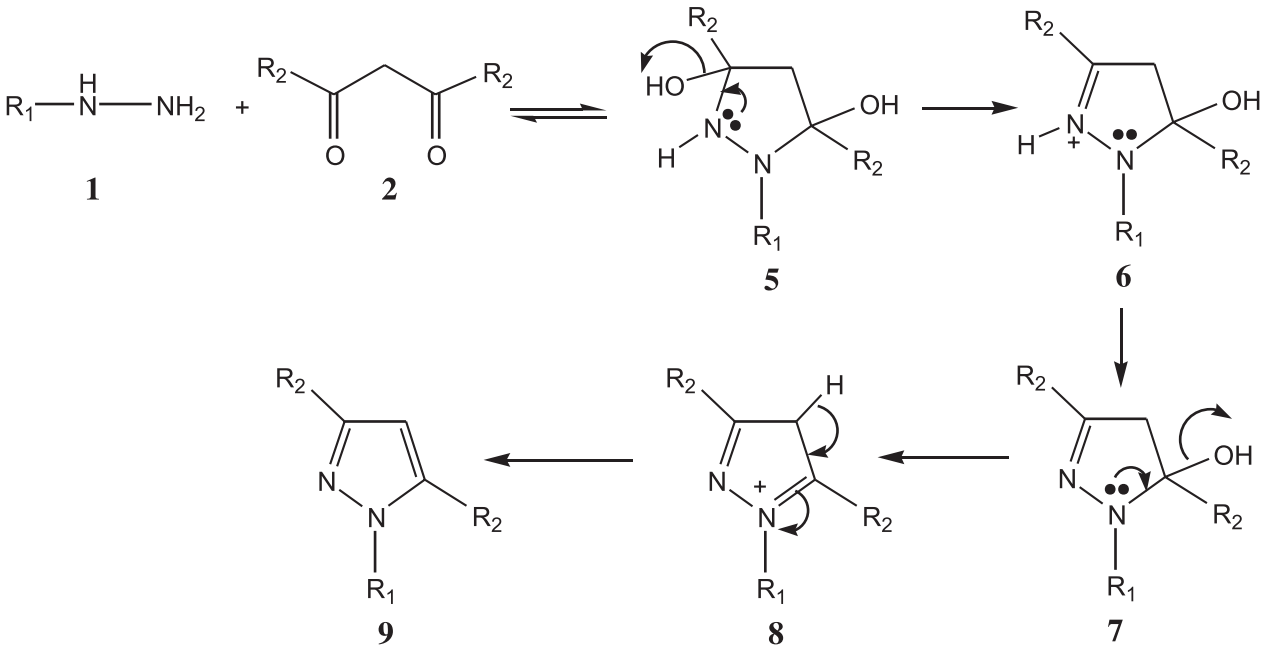


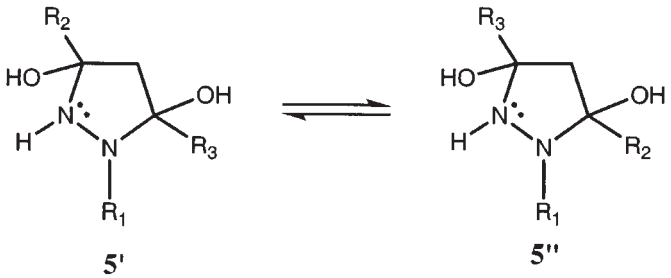
Table 1. Summary of the most relevant results related to the mechanism of the reaction between hydrazines and β-dicarbonyl compounds.

	R_1	R_2	R_3	Isolation of 5-hydroxy-pyrazoline **7**	Dehydration to pyrazole 3-CF_3 **4** and (or) 5-CF_3 **3**	Ratio **4**:**3** or **4**:**7**	Ref.
a	Saccharin[a]	CH_3	CH_3	Yes	Yes (3,5-diCH_3)	—	(6)
b	C_6H_5	CH_3	CF_3	Yes[b]	Yes (5-CF_3).	5:1	(7)
b	C_6H_5	CH_3	CF_3	Yes	No (fails, SO_4H_2)	—	(8)
c	*p*-Fluorophenyl	CH_3	CF_3	No	(5-CF_3 + 3-CF_3)	4:1	This work
d	*p*-Chlorophenyl	CH_3	CF_3	Yes[a]	Yes (5-CF_3)	4:1	(7)
e	*p*-Nitrophenyl	CH_3	CF_3	Yes **7e**	(5-CF_3) **3e**	—	This work
f	2-Benzothiazole	CH_3	CF_3	Yes	Yes (5-CF_3)	—	(9)
g	2-Quinolyl	CH_3	CF_3	Yes	Yes (5-CF_3)	—	(10)
h	Saccharin[a]	CH_3	CF_3	Yes **7h**	Yes (with loss of R_1)	—	This work
i	$CSNH_2$	Cycle[c]	CF_3	Yes	Yes (with loss of R_1)	—	(11)
j	C_6H_5	C_6H_5	CF_3	No	(3-CF_3) **4j**	—	This work
k	*p*-Fluorophenyl	C_6H_5	CF_3	No	(3-CF_3) **4k**	—	This work
l	*p*-Nitrophenyl	C_6H_5	CF_3	No	(3-CF_3) **4l**	—	This work
m	2,4-Dinitrophenyl	C_6H_5	CF_3	Yes **7m**	Yes (5-CF_3) **3m**	—	This work
n	2-Quinolyl	C_6H_5	CF_3	Yes	Yes (5-CF_3)	—	(10)
o	Saccharin[a]	C_6H_5	CF_3	Yes **7o**	Not attempted	—	This work
p	C_6H_5	2-Thienyl	CF_3	No	(3-CF_3) **4p**	—	This work
q	*p*-Fluorophenyl	2-Thienyl	CF_3	No	(3-CF_3) **4q**	—	This work
r	*p*-Nitrophenyl	2-Thienyl	CF_3	No	(3-CF_3) **4r**	—	This work
s	2,4-Dinitrophenyl	2-Thienyl	CF_3	Yes **7s**	Yes (5-CF_3) **3s**	—	This work
t	Saccharine	2-Thienyl	CF_3	Yes **7t**	Yes (with loss of R_1)	—	This work
u	*p*-Fluorophenyl	2-Pyridyl	CF_3	No	(3-CF_3) **4u**	—	This work
v	Saccharin[a]	2-Pyridyl	CF_3	Yes **7v**	Yes (with loss of R_1)	—	This work
x	$CONH_2$	CH_3	CCl_3	Yes		—	(12)
y	$CSNH_2$	CH_3	CCl_3	Yes		—	(12)
z	C_6F_5	CF_3	CF_3	Yes	Yes	—	(13,14)
aa	*p*-Fluorophenyl	CF_3	CF_3	No	(3,5-diCF_3) **9aa**	—	This work
bb	*p*-Nitrophenyl	CF_3	CF_3	Yes	Yes (3,5-diCF_3)	—	(13,14)
cc	2,4-Dinitrophenyl	CF_3	CF_3	Yes	Yes	—	(13)
dd	C_6H_5CO	CF_3	CF_3	Yes	Not reported	—	(13)
ee	2-Quinolyl	CF_3	CF_3	Yes	Yes (3,5-diCF_3)	—	(13)
ff	Saccharin[a]	CF_3	CF_3	Yes **7ff**	Yes (with loss of R_1)	—	This work

[a]Saccharin stands for 1-(1′,2′-benzisothiazol-3′-yl)-1′,1′-dioxide substituent.

[b]From the pyrrolidino adduct on the $COCF_3$.

[c]Cycle stands for a medium size carbocycle (tri, tetra, and pentamethylene pyrazoles).



The dehydration steps (**5** → **6** → **7** and **7** → **8** → **9** in Scheme 2) are irreversible, therefore, the kinetic controlling step is the first dehydration (**5** → **7**). All previous publications dealt with the influence of R_2 and R_3, i.e., the structure of the β-dicarbonyl compound, on the relative ratio of the final pyrazoles **3** and **4**, for a given hydrazine. For instance, the consequences over the **3**:**4** ratio of the fact that aldehydes (R_3 = H) are more reactive than ketones ($R_2 \neq$ H), or that trifluoromethylketones ($R_3 = CF_3$) are more reactive than ordinary ketones ($R_2 = CH_3$ or C_6H_5) have been widely studied.

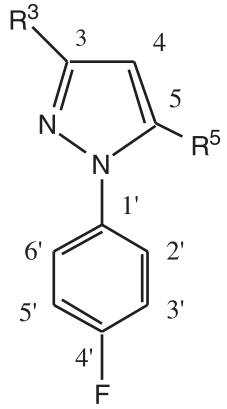
We will discuss, in the present paper, the effect of R_1 on the **3**:**4** ratio in the case of trifluoromethyl β-diketones and, particularly, when $R_2 = CH_3$ and $R_3 = CF_3$. When R_1 = H, **3** ≡ **4** due to the prototropic tautomerism of pyrazoles.

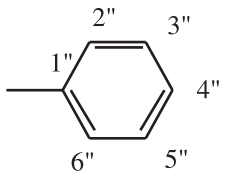
Results and discussion

We have gathered in Table 1 the most relevant experimental results for the present work, that is, the isolation of different 5-hydroxypyrazolines (**7**), the dehydration to the corresponding pyrazoles (**9**) (**3**, $R_2 = CH_3$, Ar or Het, $R_3 = CF_3$; **4**, $R_2 = CF_3$, $R_3 = CH_3$, Ar or Het) and the orientation of the reaction (**3**:**4** ratio).

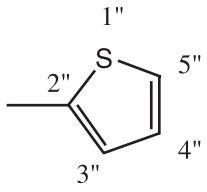
In the present work, we report complementary experiments (marked "this work" in Table 1). This leads us to describe a series of new Δ^2-pyrazolines and pyrazoles, which have been fully characterized by ^{1}H NMR and mass spectrometry (see experimental part). Particularly important for this purpose have been ^{13}C (Table 2) and ^{19}F NMR (Table 3)

Table 2. ^{13}C chemical shifts (ppm) and ^{13}C – ^{19}F coupling constants (Hz) of *p*-fluorophenylpyrazoles **3c**, **4c**, **9bb**, **4l**, **4r**, **4v**.

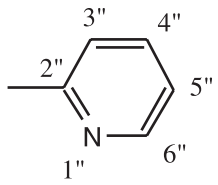




4l



4r



4v

Comp	R^3	R^5	C_3	C_4	C_5	$C_{1'}$	$C_{2'(6')}$	$C_{3'(5')}$	$C_{4'}$	R^3	R^5	$C_{1''}$	$C_{2''}$	$C_{3''}$	$C_{4''}$	$C_{5''}$	$C_{6''}$
3c	CH_3	CF_3	143.32	108.56	149.07	134.93	127.23	116.30	163.83	13.19	121.05	—	—	—	—	—	—
					J = 38		*J* = 10	*J* = 21	*J* = 251		*J* = 269						
4c	CF_3	CH_3	142.75	104.49	140.80	134.91	127.22	116.20	162.38	121.31	12.11	—	—	—	—	—	—
			J = 39				*J* = 9	*J* = 22	*J* = 250	*J* = 268							
9aa	CF_3	CF_3	142.74	107.15	134.81	134.20	127.89	116.41	163.35	119.60	118.71	—	—	—	—	—	—
			J = 43		*J* = 42		*J* = 10	*J* = 23	*J* = 251	*J* = 269	*J* = 270						
4k	CF_3	Phenyl	143.55	105.85	145.08	135.65	127.59	116.36	162.44	121.52	—	129.21	129.43	129.06	129.06	129.06	129.43
			J = 39				*J* = 9	*J* = 24	*J* = 250	*J* = 270							
4q	CF_3	2-Thienyl	143.19	105.00	138.92	134.91	128.27	116.23	162.73	121.59		S	129.36	127.64	128.17	127.57	—
			J = 39				*J* = 9	*J* = 22	*J* = 250	*J* = 268							
4u	CF_3	2-Pyridyl	143.96	106.69	150.00	135.78	127.47	116.09	162.34	121.14		N	148.05	123.60	136.70	122.93	150.00
			J = 43				*J* = 9	*J* = 23	*J* = 250	*J* = 270							

Scheme 3.

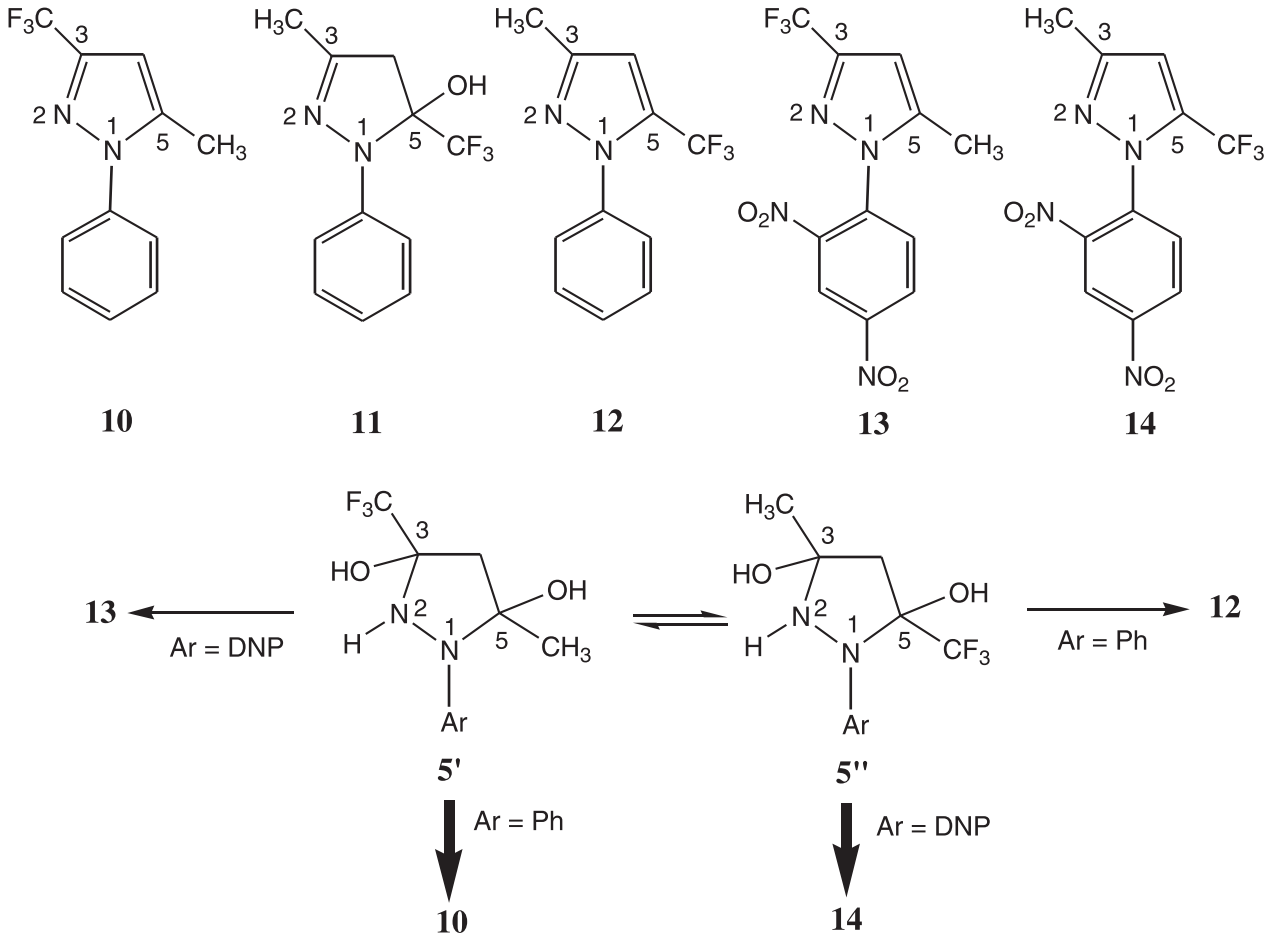


Table 3. ^{19}F chemical shifts (ppm) of some pyrazoles and 5-hydroxypyrazolines.

Comp	CF_3 position	CF_3	*p*-Fluorophenyl
3c	5	–58.2	–112.2
4c	3	–62.8	–112.6
4k	3	–62.8	–112.8
4l	3	–62.9	—
4q	3	–62.8	–111.4
4u	3	–62.7	–110.1
7e	5	–71.2	—
7h	5	–79.3	—
7s	5	–72.1	—
7ff	3	–71.2	—
	5	–78.2	—
9aa	3	–63.0	–110.0
	5	–58.7	—

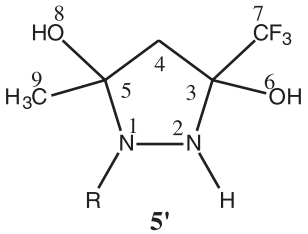
data since they are characteristic of the different structures (5, 7–10, 12–14).

The mechanism of the reaction of β-dicarbonyl compounds and hydrazines has been studied in several occasions, particularly by Selivanov and Ershov and co-workers (15–19), who first used stop-flow NMR techniques to characterize the 3,5-dihydroxypyrazolidines **5** and the 5-hydroxypyrazolines **7** as intermediates and by Elguero and Yranzo (20) who first isolated a 3,5-dihydroxypyrazolidine (**5**, R_1 = H, R_2 = R_2 = CF_3). Russian authors (21, 22) have reported further studies and the reaction has been reviewed (23–25). We have proposed that the dehydration **7** → **9** involves the intermediate **8** to explain why when R_1 is an electron-withdrawing group, the dehydration does not occur or occurs with difficulty (3, 20). Besides, 4-hydroxy-Δ^2-pyrazolines are much more stable than the 5-hydroxy ones and more difficult to aromatize (26).

The results gathered in Table 1 are fully consistent with the role of CF_3 or, more generally, perfluoroalkyl substituents at position 5 and with electron-withdrawing substituents at position 1 to stabilize the 5-hydroxypyrazolines **7**. The role of a 5-trifluoromethyl group is apparent in experiments **b**, **d**, and **z**; that of R_1 in experiment **a** (for brevity's sake, we will use saccharin instead of 1-(1′,2′-benzisothiazol-3′-yl)-1′,1′-dioxide) and that of both in many cases (**e**–**i**, **m**–**o**, s, **t**, **v**, **bb**–**ff**). Note that the CCl_3 group behaves similarly to the CF_3 group (experiments **x** and **y**).

The most difficult point is to rationalize the orientation or **4**:**3** ratio. To advance in this direction, we have carried out a series of semi-empirical calculations, using the PM3 Hamiltonian. We have selected two cases (Scheme 3): the reaction of 1,1,1-trifluoropentane-2,4-dione with phenylhydrazine and 2′,4′-dinitrophenylhydrazine (DNPh). The first yields a mixture of 1-phenyl-3-trifluoro-methyl-5-methyl-

Table 4. PM3 calculations of 1-phenyl-3,5-dihydroxypyrazolidines.



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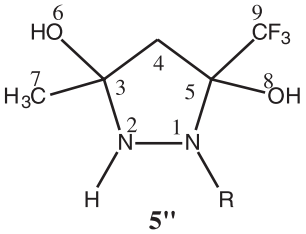

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	ΔH_f	Dipole (μ)	q-N1	q-N2	q-O6	q-O8
5′ *ddu*	**–207.7**	4.25	–0.0702	–0.0803	–0.2957	–0.3169
5′ *uuu*	–207.4	3.93	–0.0629	–0.0751	–0.2881	–0.3132
5′ *udu*	–207.2	3.31	–0.0726	–0.0503	–0.2938	–0.3061
5′ *duu*	–206.2	3.44	–0.0632	–0.0708	–0.2882	–0.3022
5′ *dud*	–204.6	3.43	–0.0325	–0.0692	–0.2875	–0.3142
5′ *ddd*	–204.6	3.76	–0.0477	–0.0352	–0.3048	–0.3138
5′ *udd*	–201.5	5.21	0.0078	–0.0365	–0.3096	–0.2716
5′ *uud*	–201.4	4.09	0.0005	–0.0657	–0.2947	–0.2801
5′′ *ddd*	**–205.2**	1.45	–0.0324	–0.0999	–0.3011	–0.2748
5′′ *uuu*	–204.6	3.17	–0.0399	–0.0422	–0.3338	–0.2864
5′′ *duu*	–203.6	4.50	–0.0461	–0.0759	–0.3121	–0.2729
5′′ *ddu*	–199.6	1.88	0.0231	–0.0862	–0.3007	–0.2566
5′′ *udu*	–197.8	1.11	0.0129	–0.0804	–0.3170	–0.2534
5′′ *udd*	–204.9	2.10	–0.0399	–0.0995	–0.3098	–0.2722
5′′ *uud*	–203.7	2.47	–0.0483	–0.0937	–0.3072	–0.2819
5′′ *dud*	–204.0	2.31	–0.0539	–0.0949	–0.2986	–0.2795

Note: ***u*** = up, ***d*** = down.

pyrazole **10** and 1-phenyl-3-methyl-5-trifluoromethyl-5-hydroxypyrazoline **11** in a ratio 5:1 (see Table 1, example **b**) (7) (*p*-fluorophenylhydrazine, example **c** behaves similarly). The pyrazoline can be dehydrated with $HCl–CH_2Cl_2$ into pyrazole **12** (7) although other authors failed using H_2SO_4 (8). From DNPh only 1-(2′,4′-dinitrophenyl)-3-methyl-5-trifluoro-methylpyrazole **14** should be formed considering the **3m** or **3s** examples of Table 1.

The first hypothesis we tested was a thermodynamical control related to the equilibrium **5′**–**5′′** between the 3,5-dihydroxypyrazolidines (Scheme 3). The problem is rather complicated because these compounds present three stereogenic centers N1, C3, and C5 (the inversion at the nitrogen atoms has very low barriers and only that bearing the phenyl ring was considered). The equilibrium between **5′** and **5′′** through the β-diketone implies the epimerization of C3 and C5. In addition, in the case of the dinitrophenyl derivatives, two conformations of this substituent, depending on which side the *o*-nitro group lies, have to be considered. Therefore, 16 and 32 conformations were calculated in the cases of Ar = C_6H_5 and Ar = 2′,4′-$(NO_2)_2$-C_6H_4, respectively. The results are given in Tables 4 and 5, which contain heats of formation (in kcal mol^{-1}), dipole moments μ (in D), and charges (q) of N1, N2, O6, and O8 atoms.

In the case of the phenyl derivative, the most stable structure is **5′** (Ar close to the CH_3) with the conformation represented in Fig. 1 (i.e., Ph *up*, 3-OH *down* and 5-OH *down* (**5′*udd***), –207.7 kcal mol^{-1}). The most stable amongst **5′′** structures is **5′′*ddd***, but it lies 2.5 kcal mol^{-1} higher.

The sixteen values of PM3 heats of formation can be expressed using an additive model with contributions of the different structural features of the compounds. In the **5′** series, a phenyl down is 0 and up is 1 while in the **5** series there is, respectively, 0 and –1. The OH substituents at the 5 position (that close to the phenyl group) is 0 when down and 1 or –1 when up for **5′** and **5′′**. When the Ph and CF_3 substituents are on the same side of the molecule, *cis*, or on opposite sides, *trans*, 1 or 0. The resulting eq. [1] for 16 compounds has an $R^2 = 0.935$

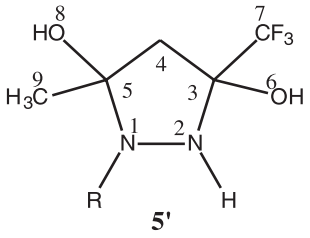
$$[1] \quad \Delta H_f = -(205.2 \pm 0.3) + (3.6 \pm 0.3)\ \text{Ph} - (1.6 \pm 0.3)\ 5\text{OH} + (2.5 \pm 0.4)\ CF_3/\text{Ph}$$

That is, the intercept is close to the average heat of formation for the sixteen compounds. The *N*-phenyl substituent prefers to be down in the **5′** series and up in the **5′′** ones, otherwise it destabilizes the compound by 3.6 kcal mol^{-1}. The contrary happens with the 5-hydroxy substituent, but the effect is lower. Finally, the presence of CF_3 and Ph groups on the same side, *cis*, destabilizes the molecule by an amount of 2.5 kcal mol^{-1}.

Since **5′*udd*** is more stable that **5′′*ddd***, then, if the reaction is thermodynamically controlled, the resulting *N*-phenylpyrazole should have been **10**, which is consistent with the experiment.

A similar analysis of the thirty-two dinitrophenyl derivatives (DNP), show that, here, the additive model is much less satisfactory (eq. [2], $n = 32$, $R^2 = 0.56$), but the effects are

Table 5. PM3 calculations of 1-(2′,4′-dinitrophenyl)-3,5-dihydroxypyrazolidines.



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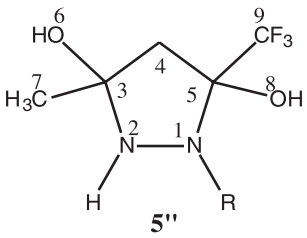


5''

	ΔH_f	Dipole μ	q-N1	q-N2	q-O6	q-O8
5′*ddda*	–211.4	6.49	–0.0700	–0.0571	–0.2730	–0.3404
5′*udda*	**–220.4**	4.28	–0.1068	–0.0793	–0.2900	–0.3149
5′*ddua*	–211.6	5.55	–0.0587	–0.0939	–0.2857	–0.3448
5′*udua*	–218.5	4.04	–0.1001	–0.0668	–0.2868	–0.2996
5′*duda*	–208.1	4.39	–0.0871	–0.0187	–0.3002	–0.2862
5′*uuda*	–215.7	8.82	–0.0716	–0.0640	–0.2962	–0.2918
5′*duua*	–204.1	5.38	–0.0574	–0.0447	–0.2887	–0.2920
5′*uuua*	–217.2	4.20	–0.1115	–0.0733	–0.2792	–0.3088
5′*dddb*	–216.0	5.35	–0.0826	–0.0247	–0.3089	–0.3128
5′*uddb*	–215.6	7.17	–0.0917	–0.0925	–0.2945	–0.3066
5′*ddub*	–213.8	3.47	–0.0858	–0.0519	–0.2798	–0.3120
5′*udub*	–215.7	5.03	–0.0610	–0.0939	–0.2790	–0.2887
5′*dudb*	–214.5	6.29	–0.0837	–0.0134	–0.3173	–0.2893
5′*uudb*	–219.3	5.99	–0.1119	–0.0470	–0.2916	–0.3045
5′*duub*	–213.8	4.16	–0.0929	–0.0431	–0.2815	–0.2993
5′*uuub*	–216.9	6.67	–0.0774	–0.0929	–0.2825	–0.2930
5″*ddda*	–215.1	6.72	–0.0664	–0.1000	–0.2919	–0.2935
5″*udda*	–214.6	6.43	–0.0590	–0.0983	–0.2953	–0.3030
5″*ddua*	–212.3	3.71	–0.0984	–0.0908	–0.2894	–0.2723
5″*udua*	–209.6	1.72	–0.1038	–0.0481	–0.3054	–0.2832
5″*duda*	–215.1	7.32	–0.0731	–0.0978	–0.3011	–0.2878
5″*uuda*	–204.2	4.99	–0.0212	–0.0627	–0.3260	–0.2752
5″*duua*	–212.5	5.90	–0.0926	–0.0910	–0.3007	–0.2755
5″*uuua*	–205.3	3.93	–0.0829	–0.0339	–0.2978	–0.2798
5″*dddb*	–213.7	4.56	–0.0735	–0.0840	–0.3157	–0.3050
5″*uddb*	–208.0	6.40	–0.0165	–0.0701	–0.2902	–0.2513
5″*ddub*	–212.4	5.79	–0.0629	–0.1090	–0.2913	–0.2771
5″*udub*	–213.9	5.19	–0.0715	–0.0768	–0.3045	–0.2793
5″*dudb*	**–217.5**	3.78	–0.0931	–0.1197	–0.3041	–0.2934
5″*uudb*	–206.1	6.48	–0.0263	–0.0613	–0.3108	–0.2470
5″*duub*	–212.7	5.79	–0.0612	–0.0789	–0.3174	–0.2771
5″*uuub*	–213.2	7.30	–0.0772	–0.0345	–0.3381	–0.2819

Note: ***u*** = up, ***d*** = down, ***a*** = NO_2 towards N2.

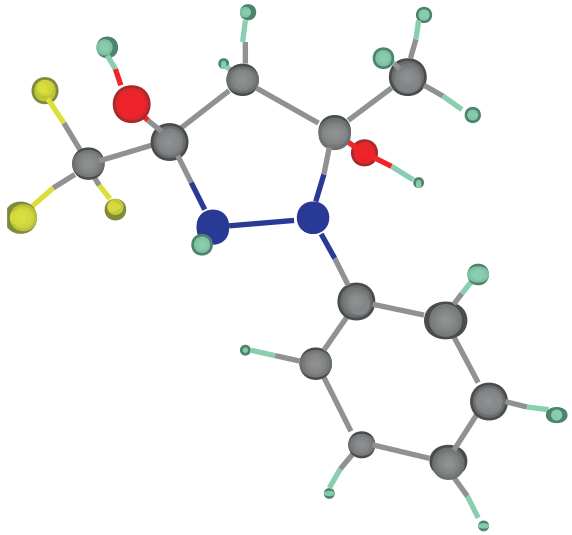
the same including a term defining the position of the nitro group (***a*** towards N2, ***b*** towards the OH).

$$[2]\quad \Delta H_f = -(212.6 \pm 0.8) + (4.3 \pm 0.9)\ \text{DNP} - (1.3 \pm 0.9)\ 5\text{OH} + (1.7 \pm 1.4)\ CF_3/\text{DNP} - (1.7 \pm 1.1)\ NO_2$$

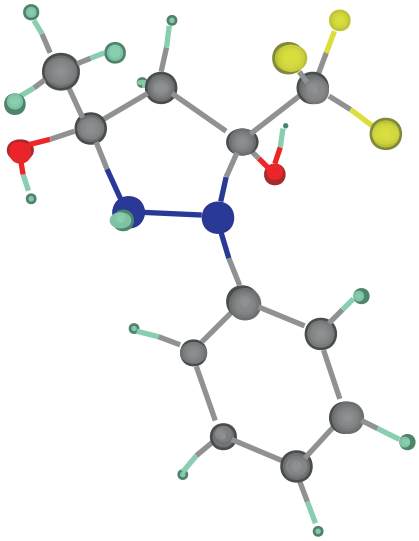
The effects are similar to those in eq. [1]: the structures are more stable when the nitro group is ***b*** in dihydroxypyrazolidines **5**″ and ***a*** in the other isomer **5**′. The two most stable compounds (see Fig. 1) are **5′*udda*** (–220.4 kcal mol^{-1}) and **5″*dudb*** (–217.5 kcal mol^{-1}). Here again, the most stable situation (2.9 kcal mol^{-1}) corresponds to the **5′** series. Consequently, isomer **13** should be formed which is contrary to experiment (formation of **14**, see Scheme 3).

Therefore, this first approach failed. Although the dipole moments are different (Tables 4 and 5), they cannot be used to explain why **14** is preferred over **12**. Since it does not seem to be a thermodynamical control we decided to explore the hypothesis of a kinetic control: the orientation of the pyrazole formation depends on the rate of dehydration of the dihydroxypyrazolidines **5**′ and **5**″. When Ar = Ph, dehydration

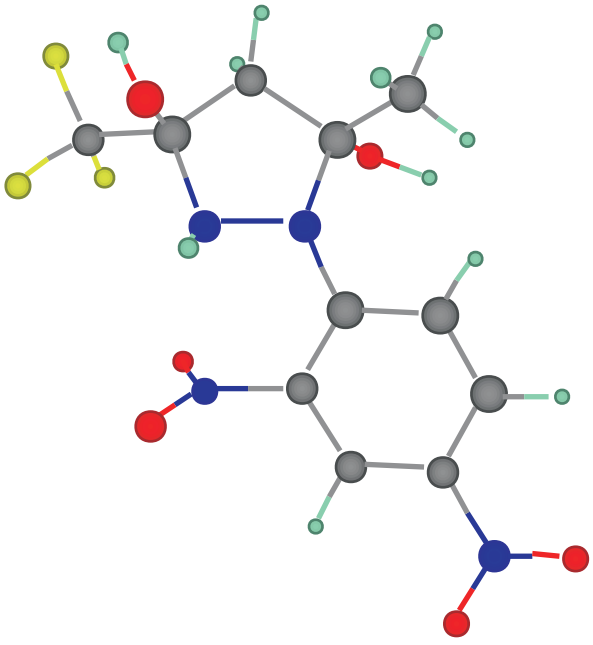
Fig. 1. Optimized PM3 structures of the isomers of minimum energy of derivatives **5′** and **5″** (**5′*udd***, **5″*ddd***, **5′*udda***, and **5″*dudb***).



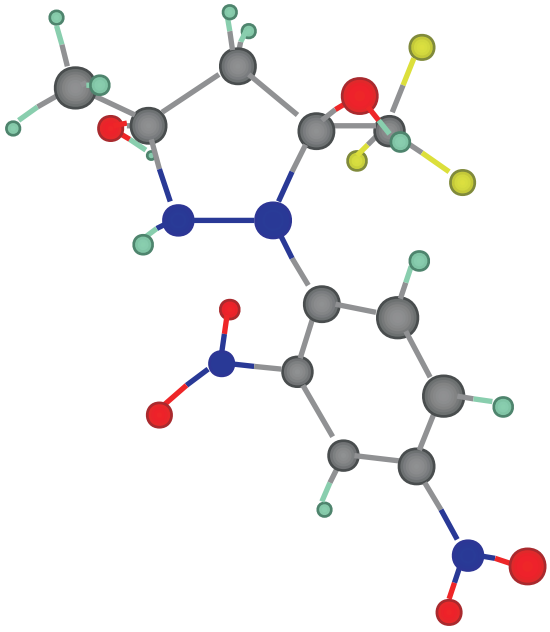
5' *udd*



5'' *ddd*



5' *udda*



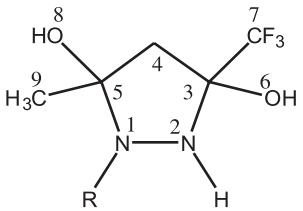
5'' *dudb*

is faster in **5′** than in **5″**; the contrary should happen when Ar = DNP.

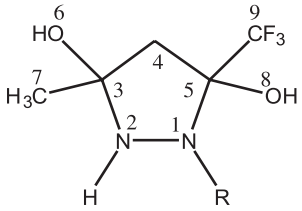
In the second case, the dehydration should involve the N2 lone pair and the OH group at position 3. Although less stable, **5″*dudb*** has more negative charge on N2 (+0.0404) and on O6 (+0.0141) than **5′*udda*** (Table 6). Consequently either neutral or assisted by protonation on O6, the easier loss of water should be that from **5″*dudb***, the less stable dihydroxypyrazolidine, yielding **14** in agreement with experimental results (see Scheme 3).

For Ar = Ph, the results are the same, i.e., the less stable dihydroxypyrazolidine **5″*ddd***, would yield **11**, which is the minor isomer, instead of **10**. Note, however, that the differences of q-N2 and q-O6 although positive are smaller

Table 6. PM3 calculations of 3,5-dihydroxypyrazolidines.



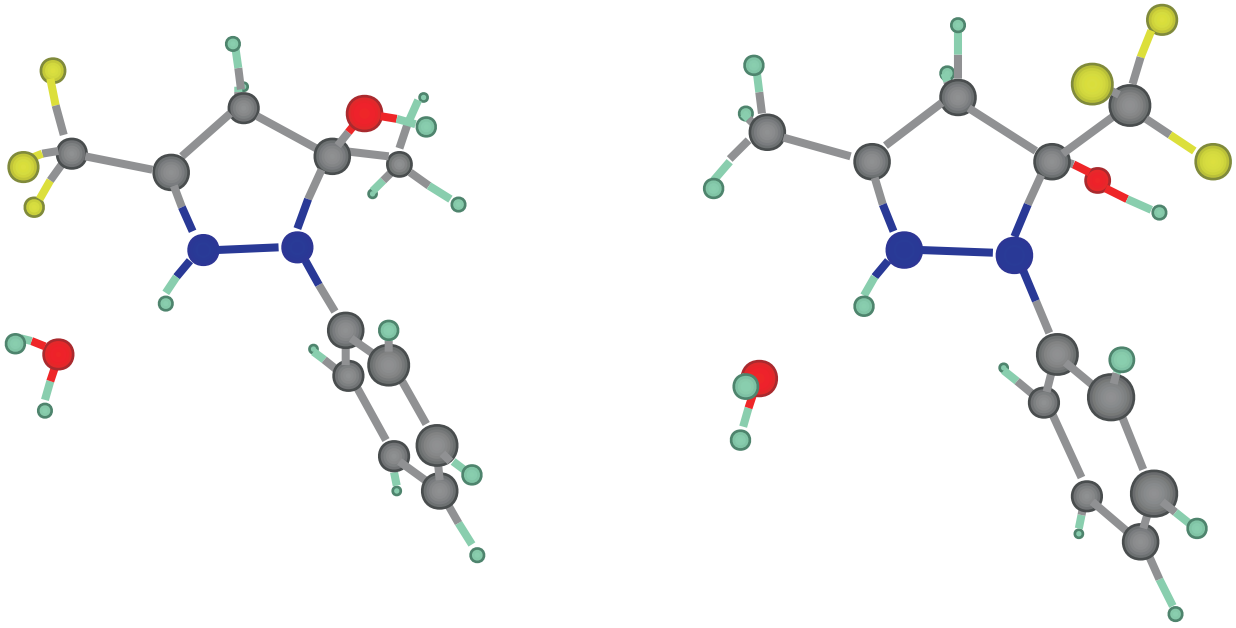
5'



5''

Comp	ΔH_f	q-N1	q-N2	q-O6	q-O8	Experimental result
5′*udd*	–207.7	–0.0702	–0.0803	–0.2957	–0.3169	**10**
5′′*ddd*	–205.2	–0.0324	–0.0999	–0.3011	–0.2748	**11**
Difference	–2.5	–0.0378	+0.0196	+0.0054	–0.0421	ratio **10**:**11** = 5:1
5′*udda*	–220.4	–0.1068	–0.0793	–0.2900	–0.3149	**13**
5′′*dudb*	–217.5	–0.0931	–0.1197	–0.3041	–0.2934	**14**
Difference	–2.9	–0.0137	+0.0404	+0.0141	–0.0215	ratio **13**:**14** = 0

Fig. 2. Optimized PM3 structures corresponding to the protonation on O6 of **5′*udd*** and **5′′*ddd*** to yield **6′*udd***·H_2O and **6′′*ddd***·H_2O.



6' *ddd* · H_2O 6" *ddd* · H_2O

(+0.0196 and +0.0054) than in the preceding case, pointing out that the preference of **11** over **10** should be smaller than that of **13** over **14**, which is what is found experimentally. It is possible that in this case, the experimental rate of formation of **10** and **11** would include the equilibrium constants between **5′*udd*** and **5′′*ddd***.

We tried to calculate the energies of the four dihydroxypyrazolidines protonated on O6 but the resulting cations are not stable and during the process of optimization, they isomerize to cations **6** (see Scheme 2) solvated by a water molecule, something like **5**$H^+ \rightarrow$ **6**·H_2O. We have represented two of such complexes, those formed from **5′*udd*** and **5″*ddd*** in Fig. 2.

Conclusions

Literature results plus those reported in this work prove that the orientation in the reaction of hydrazines with β-diketones depends on the substituent in the hydrazine. Although the differences in orientation between alkyl and arylhydrazines have been assigned to differences in reactivity of both nitrogen atoms (R_1NH, D, in alkyl- and NH_2, E, in aryl-hydrazines, see Scheme 1), this is certainly not the case of the reactions reported in Table 1, because all of them should start reacting by the NH_2. We propose that the orientation is the result of the difference in the rates of dehydration of the two 3,5-dihydroxy-pyrazolidines in equilibrium.

Experimental

Melting points were determined in open capillaries and are uncorrected. The ^{1}H NMR spectra were obtained at 270, 300, and 400 MHz, ^{13}C NMR spectra at 67.5 and 100 MHz, and ^{19}F NMR spectra at 75 and 376 MHz using Jeol-GX270, Jeol-EX400, Bruker-300, and Bruker-400 instruments. The internal standard for ^{1}H and ^{13}C was TMS and for ^{19}F NMR it was $CFCl_3$ ($\delta = 0.00$). The coupling constants reported for the ^{13}C NMR data correspond to couplings with ^{19}F. Mass spectra were recorded on a Kratos-MS-50 instrument and microanalyses were performed on a Perkin–Elmer 2400 instrument.

Synthesis of 1-(*p*-fluorophenyl)-3(5)-trifluoromethylpyrazoles

*1-p-Fluorophenyl-3-methyl-5-trifluoromethylpyrazole (**3c**) and 1-p-fluorophenyl-3-trifluoro-methyl-5-methylpyrazole (**4c**)*

An ethanolic solution (30 mL) of *p*-fluorophenylhydrazine (1 g, 6 mmol) and sodium acetate (0.5 g, 6 mmol) was refluxed for 15 min. 1,1,1-Trifluoropentane-2,4-dione (0.9 g, 6 mmol) was subsequently added and the solution was refluxed for 2 h. The solvent was evaporated and the residue obtained was extracted with chloroform. The organic phase was dried over anhydrous sodium sulfate and the chloroform was distilled off. The TLC and ^{1}H NMR of the gummy mass showed formation of both isomers in a 4:1 (**4c**:**3c**) ratio. Column chromatographic separation using silica gel (60–120 mesh) and light petroleum (60–80°) as eluent afforded **4c**.

4c: Oil, yield 0.8 g (53%). ^{1}H NMR ($CDCl_3$) δ: 2.32 (s, 3H, C_5-CH_3), 6.45 (s, 1H, C_4-H), 7.17 (unresolved dd, 2H, $C_{3'}$- and $C_{5'}$-H, J = 8.1 and 8.8 Hz), 7.42 (m, 2H, $C_{2'}$- and $C_{6'}$-H). Anal. calcd. for $C_{11}H_8F_4N_2$: C 54.11, H 3.30, N 11.47; found C 53.92, H 3.28, N 11.21.

Further elution of the column with light petroleum afforded the other isomer **3c**.

3c: Oil, yield 0.2 g (13%). ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, C_3-CH_3), 6.59 (s, 1H, C_4-H), 7.25 (unresolved dd, 2H, $C_{3'}$- and $C_{5'}$-H, J = 8.2 and 8.7 Hz), 7.42 (m, 2H, $C_{2'}$- and $C_{6'}$-H). Anal. calcd. for $C_{11}H_8F_4N_2$: C 54.11, H 3.30, N 11.47; found C 54.05, H 3.13, N 11.34.

Three other pyrazoles **4k**, **4q**, **4u** were prepared and purified similarly.

*1-p-Fluorophenyl-3-trifluoromethyl-5-phenylpyrazole (**4k**)*

Mp 102–103°C, yield 72%. ^{1}H NMR ($CDCl_3$) δ: 6.74 (s, 1H, C_4-H), 7.18–7.22 (m, 2H, $C_{2''}$- and $C_{6''}$-H), 7.30 (m, 5H, Ar-H, $C_{3''}$- $C_{4''}$- $C_{5''}$-, $C_{2'}$-, and $C_{6'}$-H), 7.03 (unresolved dd, 2H, $C_{3'}$- and $C_{5'}$-H, J = 8.1 and 8.8 Hz). Anal. calcd. for $C_{16}H_{10}F_4N_2$: C 62.75, H 3.27, N 9.15; found C 62.67, H 3.41, N 8.84.

*1-p-Fluorophenyl-3-trifluoromethyl-5-(2′-thienyl)pyrazole (**4q**)*

Mp 81–82°C, yield 74%. ^{1}H NMR ($CDCl_3$) δ: 6.70 (s, 1H, C_4-H), 6.78 (dd, 1H, $C_{3''}$-H, J = 1.0 and 3.7 Hz), 6.88 (dd, 1H, $C_{4''}$-H, J = 3.7 and 5.0 Hz), 7.03 (unresolved dd, 2H, $C_{3'}$- and $C_{5'}$-H, J = 8.1 and 8.8 Hz), 7.23 (dd, 1H, $C_{5''}$-H, J = 1.0 and 5.0 Hz), 7.28 (m, 2H, $C_{2'}$- and $C_{6'}$-H). Anal. calcd. for $C_{14}H_8F_4N_2S$: C 53.85, H 2.58, N 8.97; found C 54.02, H 2.46, N 8.63.

*1-p-Fluorophenyl-3-trifluoromethyl-5-(2′-pyridyl) pyrazole (**4u**)*

Mp 72–74°C, yield 73%. ^{1}H NMR ($CDCl_3$) δ: 7.01 (s, 1H, C_4-H), 7.08 (m, 2H, $C_{3'}$- and $C_{5'}$-H, J = 8.1 and 8.8 Hz), 7.22–7.35 (m, 4H, $C_{3''}$-, $C_{5''}$-, $C_{2'}$- and $C_{6'}$-H), 7.64 (unresolved dd, 1H, $C_{4''}$-H, J = 1.8 and 7.8 Hz), 8.58 (dd, 1H, $C_{6''}$-H, J = 3.9 and 7.8 Hz). Anal. calcd. for $C_{15}H_9F_4N_3$: C 58.64, H 2.95, N 13.68; found C 58.39, H 3.00, N 13.54.

Synthesis of 1-phenyl-3-trifluoromethylpyrazoles

*1,5-Diphenyl-3-trifluoromethylpyrazole (**4j**)*

An ethanolic solution (30 mL) of phenylhydrazine (0.64 g, 6 mmol) and sodium acetate (0.5 g, 6 mmol) was refluxed for 15 min. An equimolar amount of benzoyltrifluoroacetone (0.9 g, 6 mmol) was subsequently added and the solution was refluxed for 3 h. On cooling, a solid appeared which was recrystallized from ethanol, mp 80°C (lit. (27) mp 95°C), yield 50%. ^{1}H NMR ($CDCl_3$) δ: 6.80 (s, 1H, C_4-H), 6.85 (d, 2H, $C_{3''}$- and $C_{5''}$-H), 6.36 (dd, 1H, $C_{4''}$-H), 7.31 (dd, 2H, $C_{2''}$- and $C_{6''}$-H), 7.42–7.47 (m, 5H, Ar-H). M^+ 288. Anal. calcd. for $C_{16}H_{11}F_3N_2$: C 66.66, H 3.85, N 9.72; found C 66.47, H 3.81; N 9.70.

*1-Phenyl-3-trifluoromethyl-5-thienylpyrazole (**4p**)*

This compound was prepared similarly from thienoyltrifluoroacetone, mp 92°C, yield 51%. ^{1}H NMR ($CDCl_3$) δ: 6.75 (s, 1H, C_4-H), 7.20–7.37 (m, 8H, Ar-H). M^+ 294. Anal. calcd. for $C_{14}H_9F_3N_2S$: C 57.14, H 3.08, N 9.52; found C 57.33, H 3.17, N 9.36.

Synthesis of 1-*p*-nitrophenyl-3-trifluoromethylpyrazoles

*1-p-Nitrophenyl-3-trifluoromethyl-5-phenylpyrazole (**4l**)*

An ethanolic solution (30 mL) of *p*-nitrophenylhydrazine (0.95 g, 6 mmol) and sodium acetate (0.5 g, 6 mmol) was refluxed for 15 min. An equimolar amount of benzoyltrifluoroacetone was subsequently added and the solution was refluxed for 4 h. After solvent evaporation, the residue obtained was crystallized from ethanol, mp 91°C, yield 62%. ^{1}H NMR ($CDCl_3$) δ: 6.79 (s, 1H, C_4-H), 7.23–7.52 (m, 5H, Ar-H), 7.50 (d, 2H, $C_{2'}$- and $C_{6'}$-H), 8.22 (d, 2H, $C_{3'}$- and $C_{5'}$-H). M^+ 333. Anal. calcd. for $C_{16}H_{10}F_3N_3O_2$: C 57.66, H 3.02, N 12.61; found C 57.81, H 2.88; N 12.71.

*1-p-Nitrophenyl-3-trifluoromethyl-5-(2-thienyl)pyrazole (**4r**)*

This compound was prepared similarly from thienoyltrifluoroacetone, mp 97°C, yield 60%. ^{1}H NMR (CDCl3) δ: 6.84 (s, 1H, C_4-H), 6.93 (dd, 1H, $C_{3''}$-H), 7.04 (dd, 1H, $C_{4''}$-H), 7.44 (dd, 1H, $C_{5''}$-H), 7.69 (dd, 1H, $C_{2'}$- and $C_{6'}$-H), 8.28 (dd, 1H, $C_{3'}$- and $C_{5'}$-H). M^+ 339. Anal. calcd. for $C_{14}H_8F_3N_3O_2S$: C 49.56, H 2.38, N 12.38; found C 49.51, H 2.18, N 12.67.

*1-p-Nitrophenyl-3-methyl-5-trifluoromethyl-5-hydroxypyrazoline (**7e**)*

An ethanolic solution (30 mL) of *p*-nitrophenylhydrazine (0.95 g, 6 mmol) and sodium acetate (0.5 g, 6 mmol) was refluxed for 15 min. An equimolar amount of 1,1,1-trifluoropentane-2,4-dione (0.9 g, 6 mmol) was subsequently added and the solution was refluxed for 2 h. After solvent evaporation, the residue obtained was crystallized from ethanol, mp 102°C, yield 54%. ^{1}H NMR ($CDCl_3$) δ : 2.09 (s, 3H,

CH_3), 3.21 and 3.46 (AB system, 2H, CH_2, J = 18 Hz), 7.42 (d, 2H, $C_{2'}$- and $C_{6'}$-H), 8.04 (d, 2H, $C_{3'}$- and $C_{5'}$-H). M^+ 289. Anal. calcd. for $C_{11}H_{10}F_3N_3O_3$: C 45.68, H 3.48, N 14.53; found C 45.81, H 3.60, N 14.68.

*1-p-Nitrophenyl-3-methyl-5-trifluoromethylpyrazole (**3e**)*

An ethanolic solution of (**7e**) and 2 mL of conc. HCl was refluxed for 10 h. The solvent was evaporated and the residue crystallized from ethanol, mp 80–81°C, yield 56%. ^{1}H NMR ($CDCl_3$) δ: 2.36 (CH_3), 6.54 (s, 1H, C_4-H), 7.72 (d, 2H, $C_{2'}$- and $C_{6'}$-H), 8.33 (d, 2H, $C_{3'}$- and $C_{5'}$-H). M^+ 271. Anal. calcd. for $C_{11}H_8F_3N_3O_2$: C 48.72, H 2.97, N 15.49; found C 49.01, H 3.11, N 15.39.

*1-(1′,2′-Benzisothiazol-3′-yl)-3-methyl-5-trifluoromethyl-5-hydroxypyrazoline 1′,1′-dioxide (**7h**)*

An ethanolic solution (50 mL) of 3-hydrazino-2-benzisothiazole-1′,1′-dioxide (1.2 g, 6 mmol) and sodium acetate (0.5 g, 6 mmol) was refluxed for 15 min. An equimolar amount of 1,1,1-trifluoropentane-2,4-dione (0.9 g, 6 mmol) was subsequently added and the solution was refluxed for 2 h. The solvent was evaporated and the residue extracted with chloroform. The organic phase was dried over anhyd sodium sulfate and the chloroform distilled off, mp 180°C (ethanol), yield 54%. ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 2.14 (CH_3), 3.38 (m, 2H, CH_2), 7.72–7.83 (m, 3H, $C_{5'}$-, $C_{6'}$-, and $C_{7'}$-H), 8.67 (m, 1H, $C_{4'}$-H). M^+ 333. Anal. calcd. for $C_{12}H_{10}F_3N_3O_3S$: C 43.25, H 3.02, N 12.61; found C 43.38, H 2.87, N 12.45.

*1-(2′,4′-Dinitrophenyl)-3-phenyl-5-trifluoromethyl-5-hydroxypyrazoline (**7m**)*

An ethanolic solution (50 mL) of 2,4-dinitrophenylhydrazine (0.95 g, 6 mmol) and sodium acetate (0.5 g, 6 mmol) was refluxed for 15 min. An equimolar amount of benzoyltrifluoroacetone (0.9 g, 6 mmol) was subsequently added and the solution was refluxed for 4 h. The solvent was evaporated and the residue crystallized from ethanol, mp 142°C, yield 54%. ^{1}H NMR ($CDCl_3$) δ: 4.51 (m, 2H, CH_2), 7.38–7.99 (m, 5H, ArH), 8.06 (d, 1H, $C_{6'}$-H), 8.45 (dd, 1H, $C_{5'}$-H), 9.05 (d, 1H, $C_{3'}$-H). M^+ 396. Anal. calcd. for $C_{16}H_{11}F_3N_4O_5$: C 48.49, H 2.80. N 14.14; found C 48.22, H 2.66, N 13.81.

*1-(2′,4′-Dinitrophenyl)-3-phenyl-5-trifluoromethylpyrazole (**3m**)*

To a solution of **7m** (0.2 g, 0.5 mmol) in acetic acid was added 2 mL of pure sulfuric acid. The mixture was refluxed for 24 h. The solvent was evaporated and the residue was extracted with chloroform. The organic phase was dried over anhyd sodium sulfate and the chloroform distilled off, mp 56°C (ethanol), yield 53%. ^{1}H NMR ($CDCl_3$) δ: 6.84 (s, 1H, C_4-H), 7.30 (m, 1H, $C_{6'}$-H), 7.92 (d, 1H, $C_{5'}$-H), 8.06–9.05 (m, 6 H, Ar-H). M^+ 378. Anal. calcd. for $C_{16}H_9F_3N_4O_4$: C 50.80, H 2.40, N 15.07; found C 50.66, H 2.37, N 14.86.

*1-(1′,2′-Benzisothiazole-1′,1′-dioxide)-3-phenyl-5-trifluoromethyl-5-hydroxypyrazoline (**7o**)*

With the same method used in the case of **7i**, compound **7o** was obtained, mp 160°C (ethanol), yield 48%. ^{1}H NMR ($CDCl_3$) δ: 3.35 and 3.69 (AB system, 2H, CH_2, J = 18 Hz), 7.26–7.42 (m, 5H, Ar-H), 7.75–7.82 (m, 3H, $C_{5'}$-, $C_{6'}$-, and $C_{7'}$-H), 8.53 (s, 1H, $C_{4'}$-H). M^+ 395. Anal. calcd. for $C_{17}H_{12}F_3N_3O_3S$: C 51.65, H 3.06, N 10.63; found C 51.42, H 321, N 10.65.

*1-(2′,4′-Dinitrophenyl)-3-(2-thienyl)-5-trifluoromethyl-5-hydroxypyrazoline (**7s**)*

This compound was prepared using the procedure described for **7m**, mp 152°C, yield 58%. ^{1}H NMR ($CDCl_3$) δ: 4.42 (m, 2H, CH_2), 7.28 (m, 1H, $C_{3''}$-H), 7.92 (d, 1H, $C_{4''}$-H), 8.02 (d, 1H, $C_{5''}$-H), 8.04 (d, 1H, $C_{6'}$-H), 8.44 (dd, 1H, $C_{5'}$-H), 9.07 (d, 1H, $C_{3'}$-H). Anal. calcd. for $C_{14}H_9F_3N_4O_5S$: C 41.80, H 2.25, N 13.93; found C 42.03, H 2.41, N 13.71.

*1-(2′,4′-Dinitrophenyl)-3-(2-thienyl)-5-trifluoromethylpyrazole (**3s**)*

Following the same procedure as described for **3m**, compound **3s** was prepared, mp 61°C, yield 53%. ^{1}H NMR ($CDCl_3$) δ: 6.88 (s, 1H, C_4-H), 6.92–7.80 (m, 5H, ArH), 7.90 (d, 1H, $C_{6'}$-H), 8.66 (m, 1H, $C_{5'}$-H), 8.88 (d, 1H, $C_{3'}$-H). M^+ 384. Anal. calcd. for $C_{14}H_7F_3N_4O_4S$: C 43.76, H 1.84, N 14.58; found 43.71, H 1.56, N 14.61.

*1-(1′,2′-Benzisothiazol-3′-yl) 3-(2-thienyl)-5-trifluoromethyl-5-hydroxypyrazoline-1′,1′-dioxide (**7t**)*

With the same method used in the case of **7h**, compound **7t** was obtained, mp 190°C, yield 56%. ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 3.75 (m, 2H, CH_2), 7.5–7.7 (m, 3H, thienyl), 8.0–8.3 (m, 3H, $C_{5'}$-, $C_{6'}$-, and $C_{7'}$-H), 8.71 (m, 1H, $C_{4'}$-H). M^+ 401. Anal. calcd. for $C_{15}H_{10}F_3N_3O_3S_2$: C 44.89, H 2.51, N 10.47; found C 45.00, H 2.69, N 10.30.

*1-(1′,2′-Benzisothiazol-3′-yl)-3-(2-pyridyl)-5-trifluoromethyl-5-hydroxypyrazoline 1′,1′-dioxide (**7v**)*

With the same method used in the case of **7h**, compound **7v** was obtained, mp 224°C, yield 67%. ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 3.70 (AB system, 2H, CH_2, J = 19 Hz), 7.70–7.90 (m, 3H, $C_{5'}$-, $C_{6'}$-, and $C_{7'}$-H), 8.70–8.80 (m, 5H, pyridine and C_4-H of the benzisothiazolyl). M^+ 396. Anal. calcd. for $C_{16}H_{11}F_3N_4O_3S$: C 48.49, H 2.80, N 14.14; found C 48.36, H 2.71, N 13.85.

*1-(1′,2′-Benzisothiazol-3′-yl)-3,5-bis-trifluoromethyl-5-hydroxypyrazoline 1′,1′-dioxide (**7ff**)*

Using the same method as in the case of **7h**, compound **7ff** was obtained, mp 208°C (ethanol), yield 54%. ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 3.27 (m, 2H, CH_2), 7.8–7.9 (m, 3H, $C_{5'}$-, $C_{6'}$-, and $C_{7'}$-H), 8.46 (m, 1H, $C_{4'}$-H). M^+ 387. Anal. calcd. for $C_{12}H_7F_6N_3O_3S$: C 37.22, H 1.82, N 10.85; found C 36.98, H 2.07, N 10.70.

*1-(p-Fluorophenyl)-3,5-bis-trifluoromethylpyrazole (**9aa**)*

This compound was prepared like **3c** and **4c** but using 1,1,1,5,5,5-hexafluoropentane-2,4-dione. Mp 54°C (ethanol), yield 65%. ^{1}H NMR ($CDCl_3$) δ: 6.97 (s, 1H, C_4-H), 7.12 (unresolved dd, 2H, $C_{3'}$- and $C_{5'}$-H, J = 8.0 and 8.9 Hz), 7.38 (m, 2H, $C_{2'}$- and $C_{6'}$-H). Anal. calcd. for $C_{11}H_5F_7N_2$: C 44.31, H 1.69, N 9.40; found C 44.28, H 1.41, N 9.12.

Computational details

All the possible isomers considered for compounds **5′** and **5″** (for both R = C_6H_5 (Ph) and R = 2′,4′-$(NO_2)_2$-C_6H_4 (DNP)), see Fig. 1 for four representative examples, have been studied at semi-empirical level, optimizing all the geometrical parameters. The different configuration of the C3 and C5 atoms of the pyrazolidine ring was considered (relative orientation of both OH groups, and of the CH_3 and CF_3 groups). Besides, considering the rotation between the rings, two different orientations for the NO_2 group in *ortho* in the dinitrophenyl derivatives were taken into account. The protonated species of the most stable of each one of the compounds (**5′** and **5″**, R = Ph and DNP) were also computed. At semi-empirical level, the PM3 Hamiltonian (28), as implemented in the MOPAC 6.0 package (29), was used increasing the precision in a factor of 100 and optimizing until a gradient of 0.01 was reached. This Hamiltonian was chosen since good results had been previously obtained predicting the "stereoselectivity" of certain Michael type reactions (for example ref. (30)). In all the cases, the corresponding heats of formation, dipole moments, and charges of the atoms involved in the possible dehydration (N1, N2, O6, and O8) were calculated and gathered in Tables 4 and 5.

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