REACTIONS OF β-AMINOENONES WITH ACETYLHYDRAZINE, SEMICARBAZIDE AND METHOXYCARBONYLHYDRAZINE. SYNTHESIS OF 1-ACETYL-, 1-CARBOXAMIDE- OR METHYL 1-CARBOXYLATED PYRAZOLE DERIVATIVES[#]

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Abstract – Acetylhydrazine, semicarbazide and methoxycarbonylhydrazine react with β-aminoenones to give regioselectively the corresponding *N*-acetyl- or *N*-carboxypyrazole derivatives. The reaction are highly regioselective and occurs *via* 5-hydroxypyrazolines which in several case can be isolated and characterized.

INTRODUCTION

We[1,2] reported the regioselective synthesis of pyrazoles by reaction of β-aminoenones with monosubstituted hydrazines, and we also studied both the reaction mechanism (Scheme 1) and some factors that determine their regioselectivity.[3] One of the competitive reactions that leads in low reactive systems to regioisomeric pyrazoles begins with the attack to the β-aminoenone by the dinucleophile from the substituted nitrogen atom.
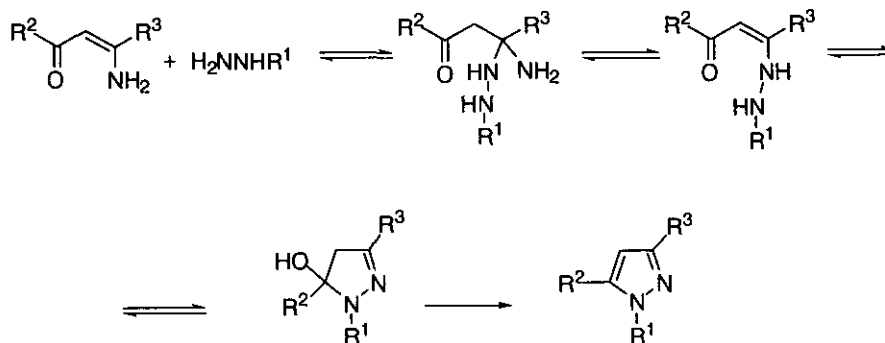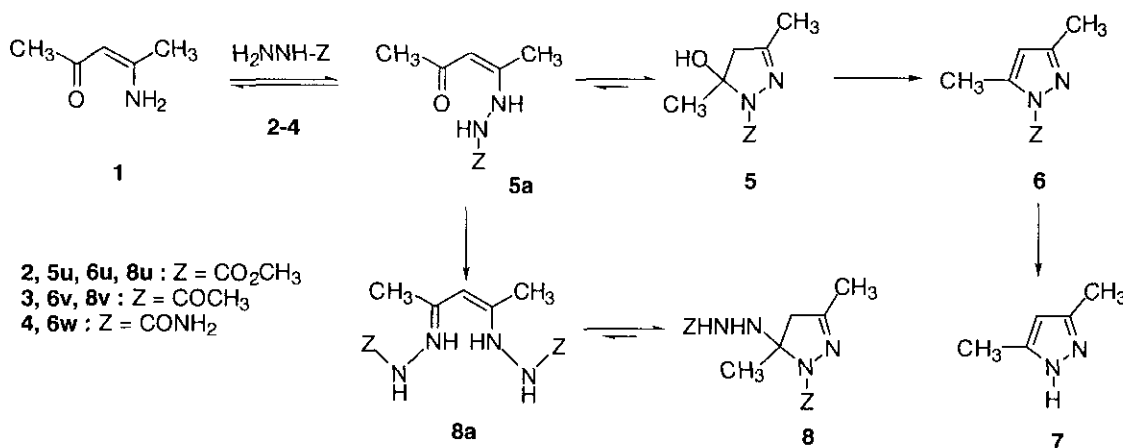

Scheme 1

We now study the reaction of β-aminoenones with monosubstituted hydrazines containing an electron-withdrawing group. The decrease of nucleophilicity at the Nα atom would make dificult its initial attack to the β-aminoenone and the progress of the main secondary reaction that determines the decrease in regioselectivity. On the other hand, the second stage in the process, wich involves the cyclization and

later aromatization of the resulting cyclic system, would be delayed. In this case, the intermediate hydroxypyrazolines, wich are only detected by ^{1}H-NMR in reactions in deuterated dimethyl sulfoxide, could be isolated and identified.

RESULTS AND DISCUSSION

The initial research was carried out with 4-amino-3-penten-2-one (**1**), which produced only one pyrazole. Their reactions with methoxycarbonylhydrazine (**2**), acetylhydrazine (**3**) and semicarbazide hydrochloride (**4**) yielded the products shown in the Scheme 2. Their relative proportions (Table 1) varied according to the time and reaction conditions, especially when hydrochloric acid was used as a catalyst. The transformation rate into **6** from the hydroxypyrazoline (**5**) did not allow its isolation. Its presence in the reaction mixture was revealed by ^{1}H NMR spectroscopy. The presence of **8** may be explained by attack of a second molecule of **2** or **3** at the ene hydrazine tautomer of the hydroxypyrazoline (**5**), in accordance with the relevant bibliography.[4]
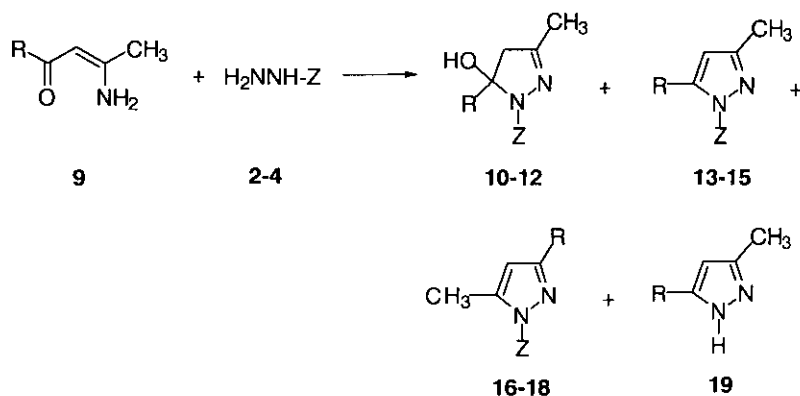

Scheme 2

Table 1. Reaction of **1** with hydrazine derivatives in ethanol solution.

Hydrazine	Time(h)	Temp.	Catalyst	Ratio 1: 2, 3 or 4	%(5)	%(6)	%(8)	%(7)
2	110	rt	AcOH	1:1.1	-	97	-	-
2	110	rt	AcOH	1:3.0	-	72	23	-
2	120	rt	HCl	1:1.1	48[a]	4	-	14
2	148	reflux	-	1:1.1	-	49	-	-
3	45	rt	AcOH	1:1.1	-	49	21 [a]	-
3	8	reflux	HCl	1:1.5	-	80	-	-
4	2	rt	-	1:1.0	-	95	-	-
4	0.5	rt	-	1:1.0	-	98	-	-

[a] Presence detected by ^{1}H NMR

a: R = PhCH$_2$CH$_2$; b: R = t-C$_4$H$_9$; c: R = 4-CH$_3$OC$_6$H$_4$; d: R = Ph; e: R = 4-O$_2$NC$_6$H$_4$
10, 13, 16: Z = CO$_2$CH$_3$; 11, 14, 17: Z = COCH$_3$; 12, 15, 18: Z = CONH$_2$.

Scheme 3

The behavior of β-aminoenones (**9**) with regard to **2**, **3** and **4** (capable of producing mixtures of regioisomer pyrazoles) is summarized in Scheme 3. The reactions are highly regioselective in the conditions used (Table 2) and are suitable for synthetic purposes. They lead to the 5-hydroxypyrazoline intermediate or to the pyrazole itself (**13-15**). In the first case the stirring of **10-12** at room temperature with a solution of hydrogen chloride in chloroform or its heating with silica gel in toluene produced **13-15** (yields over 95%).

Table 2. Reactions of β-aminoenones (**9**) with hydrazine derivatives in ethanol solution.

β-Aminoenone	Hydrazine[a]	Time(h)	Catalyst	%(10-12)	%(13-15)	%(16-18)	%(19)
9a	**2**	96	AcOH	-	70	-	30
9b	**2**	2	AcOH	54[b]	46	-	-
9c	**2**	24	AcOH	98	-	-	-
9d	**2**	18	AcOH	96	-	-	-
9e	**2**	24	AcOH	97	-	-	-
9a	**3**	7.5	AcOH	81	-	-	13
9b	**3**	16	AcOH	81	-	-	19
9c	**3**	54	AcOH	80	14[b]	-	-
9d	**3**	49	AcOH	98	-	-	-
9a	**4**	2	-	-	97	-	-
9b	**4**	6	-	24[b]	31[b]	-	45
9c	**4**	4	-	-	95	-	-
9d	**4**	6	-	-	91	3	6

[a] Molar ratio **9:2-4** = 1:1.1. [b] Presence detected by ¹H NMR.

The hydroxypyrazolines (**10-12**) are quite stable and can be easily isolated when R is an aryl group. The study of **11d** by X-Ray diffraction[5] reveals that the spacial arrangement of hydroxyl and acetyl groups (Figure 1a) allows the establishment of a hydrogen bond (Figure 1b) which stabilizes the compound.
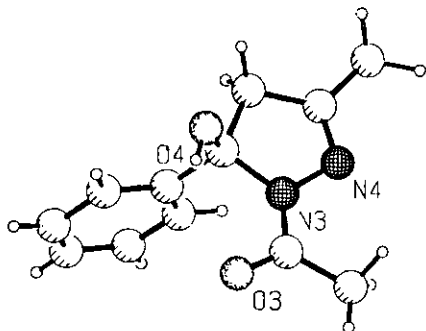

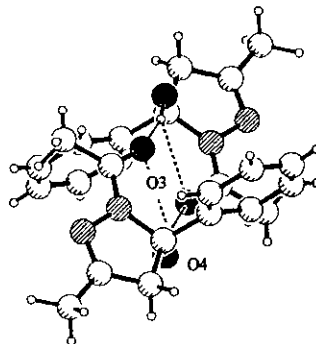**Figure 1a**   **Figure 1b**

The rate of formation of the **10-12** intermediates decreases when the size of the R group increases and grows with the capacity of the latter to release electrons. In the reactions in which **9b** takes part, the steric hindrance of the *tert*-butyl group retards the formation of **10b**. This allows us to identify the first intermediate in the sequence (**20**) -prior to the hydroxypyrazoline- and, thus, to confirm the mechanism reaction (Scheme 4).
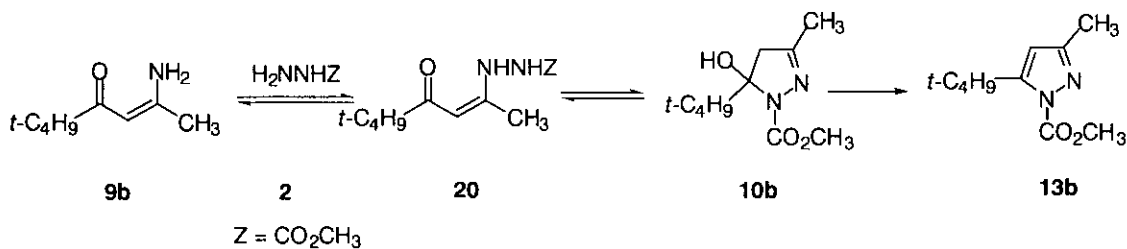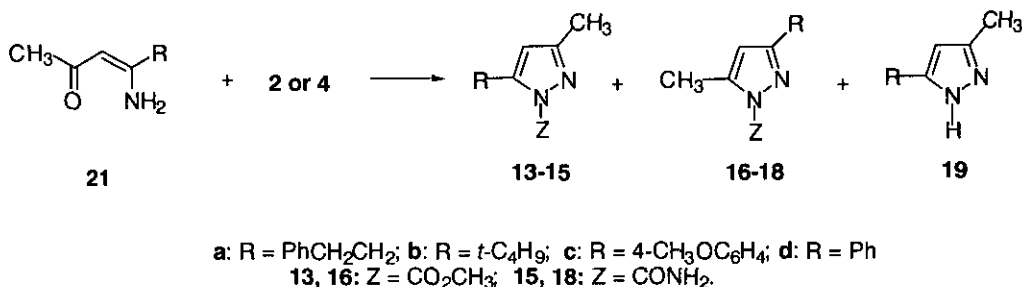

Scheme 4

Moreover, the ease of transforming **10-12** into pyrazoles varies with the size of R and with its electron-withdrawing effect, in the sense established by Zelenin[6] and Selivanov[7,8] in his study of β-diketones. In our research into the relationship between **1**, **9a** and **9b** and methoxycarbonylhydrazine by ^{1}H NMR, we have observed that the rate of pyrazole formation varies in the order Me>PhCH$_2$CH$_2$>*t*-Bu.

The presence of hydrochloric acid in the reaction system (added either as a catalyst or generated by hydrolysis of semicarbazide hydrochloride): (a) accelerates the transformation of the hydroxypyrazolines into pyrazoles, (b) may determine the partial hydrolysis of the β-aminoenone to the respective β-diketone and give rise to the corresponding mixture of the two regioisomer pyrazoles and (c) intensifies the hydrolysis and the decarboxylation of the resulting *N*-substituted pyrazole: the latter occuring to a greater extent when the time and temperature on the reaction are increased.

The β-aminoenones (**21**) are less active in relation to **2, 3** and **4** than their regioisomers (**9**) the reactions usually require a catalysis with strong acids or the use of higher temperatures and more prolonged reaction times. This implies certain restrictions with respect to their synthetic applications: among others, the production of small or negligible quantities of regioisomer pyrazole (Scheme 5, Table 3).

**a**: R = PhCH$_2$CH$_2$; **b**: R = t-C$_4$H$_9$; **c**: R = 4-CH$_3$OC$_6$H$_4$; **d**: R = Ph
13, 16: Z = CO$_2$CH$_3$; **15, 18**: Z = CONH$_2$.

Scheme 5

Table 3. Reactions of the β-aminoenones (**21**) with hydrazine derivatives.

β-Aminoenone	Hydrazine[a]	Time(h)	Temp.	Catalyst	Solv.	%(13-15)	%(16-18)	%(19)
21a	**2**	6.5	reflux	HCl	EtOH	-	100	-
21b	**2**	5	reflux	HCl	EtOH	20	80	-
21c	**2**	8	reflux	HCl	EtOH	-	100	-
21d	**2**	8	reflux	HCl	EtOH	-	100	-
21a	**4**	3	rt		Water	44	5	19[b]
21a	**4**	27	rt		EtOH	10	40[b]	-
21b	**4**	49	rt		Water	30	-	70
21b	**4**	48	rt		EtOH	29	-	55[b]
21c	**4**	26	rt		EtOH	10	90	-
21c	**4**	4	rt		Water	16	84	-
21d	**4**	6	rt		Water	10	81	9
21d	**4**	24	rt		EtOH	-	87	13

[a] Molar ratio **21 : 2-4** = 1:1.1 in the reaction without external catalyst and in those catalysed by AcOH, and 1: 1.5 when the catalyst is HCl. [b] **21** is recovered untransformed.

Given that in some cases the β-diketone is obtained through the hydrolysis of the β-aminoenone in the same reaction conditions, the loss of regioselectivity must be due, in general, to the said competitive hydrolysis, followed by the reaction of the hydrazine with the β-dicarbonyl compound. Notwithstanding the latter observation, the formation of the regioisomer which accompanies the main pyrazole when mixtures of both are produced, could take place by the isomerization of the same pyrazole. Although the isomerization processes described[9-11] refer only to transformations of 5-aryl- in 3-arylpyrazoles, we have

shown that isomerization of pyrazoles is likewise possible, under mild conditions, when the susbstituents in 3 and 5 are alkyl groups (Scheme 6).
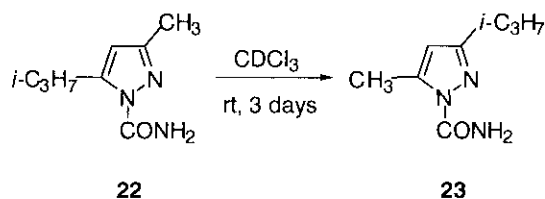
Scheme 6

Lastly, we should point out that, in relation to other synthetic methods such as the use of β-diketones or the acylation of the 1H-pyrazole, our method allows us to obtain pyrazoles of the **16-18** type which, methods known so far have not been able to synthesize.

EXPERIMENTAL

Mps were measured on a Leit Laborlux D microscope with a heating device and are uncorrected. NMR spectra were recorded on Bruker AC300 espectrometer, and chemical shifts are given downfield from SiMe$_4$ as internal standard, ^{13}C NMR spectra were carried out with complete ^{1}H decoupling and the assignments were made by additional DEPT experiments. MS spectra and elemental analyses were measured on a Hewlett-Packard 5988 A mass spectrometer and on a Perkin-Elmer 2400B analyser respectively.

The starting compounds were purchased from the usual suppliers or synthesized by literature procedures. Synthesis of **1, 9a-e** involves the condensation of ammonia with β-diketones and their isolation as only products.[12] β-Aminoenones **(21a-d)** were obtained by catalytic hydrogenation[2,13,14] of 3,5-disubstituted isoxazoles: these were prepared regioselectively by the procedure of Nitz et al.[15] from oximes and N-methoxy-N-methylalkylamides.

Preparation of methyl 1-carboxylate- and 1-acetylpyrazoles from β-aminoenones. A solution of 18 mmol of the β-aminoenone and 20 mmol of **2** or **3** in 10 mL of EtOH was refluxed for the times given on the Tables 1, 2 and 3 (50μL of HCl or 3 mL of AcOH, is added when an acid is employed as catalyst). At the end of the reaction, monitored by TLC, the solution is poured into water, and when necesary neutralized with saturated aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$, and the organic layer, dried (MgSO$_4$), and evaporated under reduced presure. When the compounds obtained are **10-11**, stirring at rt with a solution of hydrogen chloride in chloroform or heating with silica gel in toluene produced **13-14**.

The compounds (**6u, 6v, 8u, 10c, 10d, 10e, 11a, 11b, 11c, 11d, 13a, 13b, 13c, 13d, 13e, 14d, 16a, 16b, 16c** and **16d**) were thus obtained. The chemical yields and the physical spectral characteristics of these products are given below; **5u, 8v, 10b, 14c** and **20** were detected by ^{1}H NMR in the reaction mixture.

Methyl 4,5-dihydro-3,5-dimethyl-5-hydroxypyrazole-1-carboxylate (5u)

Not isolated. Detected in the mixture by ^{1}H NMR. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 1.78 (s,3H), 1.96 (s, 3H), 2.82 (d, J = 18.68, 1H), 3.01 (d, J = 18.68, 1H), 3.76 (s, 3H).

Methyl 3,5-dimethylpyrazole-1-carboxylate (6u)

97%, mp 47-48°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.15 (s, 3H), 2.41 (s, 3H), 3.90 (s, 3H), 5.86 (s, 1H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.58 (CH$_3$), 13.83 (CH$_3$), 54.10 (CH$_3$), 110.42 (CH), 144.79 (C), 150.61 (C), 152.47 (C); MS : m/z 154 (M$^+$,100). Anal. Calcd for C$_7$H$_{10}$N$_2$O$_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.53; H, 6.51; N, 18.25.

1-Acetyl-3,5-dimethylpyrazole (6v)

80%, bp 110°C /12 mmHg. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.23 (s, 3H), 2.53 (s, 3H), 2.65 (s, 3H), 5.95 (s, 1H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.75 (CH$_3$), 14.55 (CH$_3$), 23.49 (CH$_3$), 111.10 (CH), 143.92 (C), 151.90 (C), 71.40 (C); MS : m/z 138 (M$^+$100). Anal. Calcd for C$_7$H$_{10}$N$_2$O: C, 60.85; H, 7.30; N, 20.27. Found: C, 60.82; H, 7.32; N, 20.24.

Methyl 4,5-dihydro-3,5-dimethyl-5-(N′-methoxycarbonylhydrazino)pyrazole-1-carboxylate (8u)

(ratio 1:2 is 1:3) 23%, mp 80-81°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 1.67 (s, 3H), 2.00 (s, 3H), 2.74 (d, J = 18.86, 1H), 3.06 (d, J = 18.86, 1H), 3.71 (s, 3H), 3.84 (s, 3H), 4.91 (br, NH), 6.25 (br, NH); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 16.20 (CH$_3$), 23.20 (CH$_3$), 46.87 (CH$_2$), 52.70 (CH$_3$), 52.97 (CH$_3$), 82.80 (C), 152.81 (C), 154.80 (C), 157.66 (C); MS : m/z 244 (M$^+$, 6), 155 (100). Anal. Calcd for C$_9$H$_{16}$N$_4$O$_4$: C, 44.26; H, 6.60; N, 22.94 . Found: C, 44.43; H, 6.63; N, 22.86.

1-Acetyl-5-(N′-acetylhydrazine)-4,5-dihydro-3,5-dimethylpyrazole (8v).

Not isolated. Detected in the mixture by ^{1}H NMR. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.23 (s, 3H), 2.47 (s, 3H), 2.65 (s, 3H), 2.71 (s, 3H), 2.80 (d, J = 19.68, 1H), 2.99 (d, J = 19.68, 1H).

Methyl 5-t-butyl-4,5-dihydro-5-hydroxy-3-methylpyrazole-1-carboxylate (10b).

Not isolated. Detected in the mixture by ^{1}H NMR. ^{1}H NMR (300 MHz CDCl$_3$) δ = 0.89 (s, 9H), 1.93 (s, 3H), 2.78 (d, J = 18.48, 1H), 2.90 (d, J = 18.48, 1H), 3.72 (s, 3H), 5.33 (br, OH). ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 16.00 (CH$_3$), 24.82 (CH$_3$), 40.72 (C), 47.42 (CH$_2$), 53.02 (CH$_3$), 99.88 (C), 154.96 (C), 156.76 (C).

Methyl 4,5-dihydro-5-hydroxy-5-(4-methoxyphenyl)-3-methylpyrazole-1-carboxylate (10c)

93%, mp 110-112°C from hexane-toluene. ^{1}H NMR (300 MHz CDCl$_3$) δ = 2.08 (s, 3H), 2.95 (d, J = 18.66, 1H), 3.25 (d, J = 18.66, 1H), 3.80 (s, 6H), 4.50 (br, OH), 6.88-7.36 (m, 4H Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 15.90 (CH$_3$), 53.07 (CH$_3$), 53.90 (CH$_2$), 55.17 (CH$_3$), 93.26 (C), 113.86 (CH), 125.38 (CH), 135.59 (C), 152.80 (C), 153.86 (C), 159.25 (C); MS : m/z 264 (M$^+$, 22), 135 (100). Anal. Calcd for C$_{13}$H$_{16}$N$_2$O$_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.08; H, 6.07; N, 10.56.

Methyl 4,5-dihydro-5-hydroxy-3-methyl-5-phenylpyrazole-1-carboxylate (10d)

96%, mp 119-120°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.08 (s, 3H), 2.96 (d, J = 18.76, 1H), 3.25 (d, J = 18.76, 1H), 3.80 (s, 3H), 4.58 (br, OH), 7.37 (m, 5H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 15.94 (CH$_3$), 53.19 (CH$_3$), 53.90 (CH$_2$), 93.36 (C), 124.12 (CH), 128.15 (CH), 128.65 (CH), 143.40 (C), 152.91 (C), 153.85 (C); MS : m/z 234 (M$^+$, 7), 105 (100). Anal. Calcd for C$_{12}$H$_{14}$N$_2$O$_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.57; H, 6.00; N, 12.00.

Methyl 4,5-dihydro-5-hydroxy-3-methyl-5-(4-nitrophenyl)pyrazole-1-carboxylate (10e)

97%, mp 191-192°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.12 (s, 3H), 2.96 (d, J = 18.73, 1H), 3.31 (d, J = 18.73, 1H), 3.82 (s, 3H), 4.65 (br, OH), 7.61-8.27 (m, 4H Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 15.83 (CH$_3$), 53.48 (CH$_3$), 53.71 (CH$_2$), 92.64 (C), 123.96 (CH), 125.51 (CH), 147.62 (C), 150.19 (C), 153.40 (C), 153.95 (C); MS: m/z 320 (M$^+$, 7), 262 (100). Anal. Calcd for C$_{12}$H$_{13}$N$_3$O$_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.49; H, 4.67; N, 15.10.

1-Acetyl-4,5-dihydro-5-hydroxy-3-methyl-5-(2-phenylethyl)pyrazole (11a)

81%, mp 81-82°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 1.99 (s, 3H), 2.24 (s, 3H), 2.49 (m, 2H), 2.62 (m, 2H), 2.82 (d, J = 18.69, 1H), 2.90 (d, J = 18.69, 1H), 4.70 (br, OH), 7.18 (m, 5H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 16.09 (CH$_3$), 22.45 (CH$_3$), 30.90 (CH$_2$), 40.41 (CH$_2$), 48.96 (CH$_2$), 126.10 (CH), 128.33 (CH), 128.45 (CH), 140.71 (C), 154.68 (C), 170.90 (C); MS : m/z 287 (M$^+$, 11), 229 (100). Anal. Calcd for C$_{14}$H$_{18}$N$_2$O$_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.23; H, 7.39; N, 11.33.

1-Acetyl-5-t-butyl-4,5-dihydro-5-hydroxy-3-methylpyrazole (11b)

81%, mp 85-86°C from hexane. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 0.96 (s, 9H), 2.01 (s, 3H), 2.36 (s, 3H), 2.86 (d, J = 18.70, 1H), 2.94 (d, J = 18.70, 1H), 6.25 (br, OH); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 16.04 (CH$_3$), 23.21(CH$_3$), 24.91 (CH$_3$), 40.92 (C), 47.80 (CH$_2$), 101.12 (C), 157.21 (C), 172.91 (C); MS : m/z 198 (M$^+$, 2), 99 (100). Anal. Calcd for C$_{10}$H$_{18}$N$_2$O$_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.65; H, 9.13; N, 14.16.

1-Acetyl-4,5-dihydro-5-hydroxy-5-(4-methoxyphenyl)-3-methylpyrazole (11c)

80%, mp 110-111°C from diethyl ether. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.03 (s, 3H), 2.31 (s, 3H), 2.88 (d, J = 18.43, 1H), 3.26 (d, J = 18.43, 1H), 3.77 (s, 3H), 5.18 (br, OH), 6.84-7.28 (m, 4H Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 15.88 (CH$_3$), 23.08 (CH$_3$), 53.89 (CH$_2$), 55.15 (CH$_3$), 93.30 (C), 113.84 (CH), 125.20 (CH), 135.40 C), 142.90 (C), 152.63 (C), 153.71 (C); MS : m/z 248 (M$^+$, 4), 149 (100). Anal. Calcd for C$_{13}$H$_{16}$N$_2$O$_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.97; H, 6.51; N, 11.24.

1-Acetyl-4,5-dihydro-5-hydroxy-3-methyl-5-phenylpyrazole (11d)

98%, mp 117-118°C from diethyl ether. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.05 (s, 3H), 2.32 (s, 3H), 2.92 (d, J = 19.01, 1H), 3.27 (d, J = 19.01, 1H), 5.01 (br, OH), 7.35 (m, 5H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 16.00 (CH$_3$), 22.20 (CH$_3$), 54.15 (CH$_2$), 93.35 (C), 123.80 (CH), 127.97 (CH), 128.65 (CH), 143.73 (C), 154.22 (C), 170.31 (C); MS : m/z 218 (M$^+$, 36), 105 (100). Anal. Calcd for C$_{12}$H$_{14}$N$_2$O$_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.99; H, 6.43; N, 12.88.

Methyl 3-methyl-5-(2-phenylethyl)pyrazole-1-carboxylate (13a)

70%, mp 53-54°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.26 (s, 3H), 2.94 (m, 2H), 3.25 (m, 2H), 4.02 (s, 3H), 5.99 (s, 1H), 7.23 (m, 5H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.82 (CH$_3$), 29.50 (CH$_2$), 34.60 (CH$_2$), 54.34 (CH$_3$), 109.88 (CH), 126.14 (CH), 128.32 (CH), 128.38 (CH), 140.70 (C), 148.77 (C), 150.60 (C), 152.59 (C); MS : m/z 244 (M$^+$, 100). Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.69; H, 6.63; N, 11.52.

Methyl 5-*t*-butyl-3-methylpyrazole-1-carboxylate (13b)

46%, bp 85°C/0.7 mmHg. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 1.43 (s, 9H), 2.26 (s, 3H), 4.02 (s, 3H), 6.04 (s, 1H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.75 (CH$_3$), 29.18 (CH$_3$), 33.08 (C), 54.47 (CH$_3$), 109.18 (CH), 150.70 (C), 151.46 (C), 158.00 (C); MS : m/z 196 (M$^+$, 62), 181 (100). Anal. Calcd for C$_{10}$H$_{16}$N$_2$O$_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.20; H, 8.19; N, 14.25.

Methyl 5-(4-methoxyphenyl)-3-methylpyrazole-1-carboxylate (13c)

92%, mp 101-102°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.34 (s, 3H), 3.84 (s, 3H), 3.94 (s, 3H), 6.17 (s, 1H), 6.17-7.35 (m, 4H, Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.82 (CH$_3$), 54.42 (CH$_3$), 55.21 (CH$_3$), 111.84 (CH), 113.24 (CH), 122.90 (C), 130.30 (CH), 147.89 (C), 150.36 (C), 152.71 (C), 159.96 (C); MS : m/z 246 (M$^+$, 100). Anal. Calcd for C$_{13}$H$_{14}$N$_2$O$_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.30; H, 5.71; N, 11.42.

Methyl 3-methyl-5-phenylpyrazole-1-carboxylate (13d)

91%, mp 41-42°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.34 (s, 3H), 3.92 (s, 3H), 6.20 (s, 1H), 7.39 (5H, Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.80 (CH$_3$), 54.44 (CH$_3$), 112.13 (CH), 127.76 (CH), 128.77 (CH), 128.91 (CH), 130.69 (C), 147.88 (C), 150.21 (C), 152.72 (C); MS : m/z 216 (M$^+$, 100). Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_2$: C, 66.66; H, 5.59; N, 12.95. Found: C, 66.57; H, 5.59; N, 13.02.

Methyl 3-methyl-5-(4-nitrophenyl)pyrazole-1-carboxylate (13e)

93%, mp 135-137°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.39 (s, 3H), 3.98 (s, 3H), 6.34 (s, 1H), 7.57-8.29 (m, 4H Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.85 (CH$_3$), 54.88 (CH$_3$), 113.19 (CH), 123.13 (CH), 130.09 (CH), 137.19 (C), 145.44 (C), 147.90 (C), 150.19 (C), 153.15 (C); MS : m/z 290 (M$^+$, 5), 262 (100). Anal. Calcd for C$_{12}$H$_{11}$N$_3$O$_4$: C, 55.18; H, 4.24; N, 16.08. Found: C, 55.23; H, 4.26; N, 16.12.

1-Acetyl-5-(4-methoxyphenyl)-3-methylpyrazole (14c).

Not isolated. Detected in the mixture by ^{1}H NMR. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 1.89 (s, 3H), 2.22 (s, 3H), 3.88 (s, 3H), 6.12 (s, 1H), 6.93-7.98 (m, 4H Ar).

1-Acetyl–3-methyl-5-phenylpyrazole (14d)

90%, mp 38-40°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.32 (s, 3H), 2.68 (s, 3H), 6.20 (s, 1H), 7.38 (s, 5H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.72 (CH$_3$), 23.65 (CH$_3$), 112.78 (CH), 127.69 (CH), 128.47 (CH), 128.78 (CH), 131.19 (C), 146.54 (C), 151.85 (C), 170.02 (C); MS : m/z 241 (M$^+$, 2), 159 (100). Anal. Calcd for C$_{12}$H$_{12}$N$_2$O: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.05; H, 6.06; N, 13.94.

Methyl 5-methyl-3-(2-phenylethyl)pyrazole-1-carboxylate (16a)

96%, bp 205°C/1.5 mmHg. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.52 (s, 3H), 2.94 (s, 4H), 4.02 (s, 3H), 5.95 (s, 1H), 7.22 (m, 5H) ; ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 14.20 (CH$_3$), 30.21 (CH$_2$), 35.23 (CH$_2$), 54.42 (CH$_3$), 109.70 (CH), 126.09 (CH), 128.35 (CH), 128.42 (CH), 141.13 (C), 144.99 (C), 150.88 (C), 156.25 (C); MS : m/z 244 (M$^+$, 82), 91 (100). Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.83; H, 6.62; N, 11.51.

Methyl 3-*t*-butyl-5-methylpyrazole-1-carboxylate (16b)

75%, bp 120°C/2.5 mmHg. ^{1}H NMR (300 MHz, CDCl$_3$) δ =1.30 (s, 9H), 2.52 (s, 3H), 4.01 (s,3H), 6.08 (s, 1H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 14.33 (CH$_3$), 29.81 (CH$_3$), 32.32 (C), 54.42 (CH$_3$), 107.71 (CH), 144.81 (C), 151.19 (C), 165.25 (C); MS : m/z 196 (M$^+$, 28), 181 (100). Anal. Calcd for C$_{10}$H$_{16}$N$_2$O$_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.21; H, 8.23; N, 14.33.

Methyl 3-(4-methoxyphenyl)-5-methylpyrazole-1-carboxylate (16c)

95 %, mp 113-114°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.61 (s, 3H), 3.84 (s, 3H), 4.06 (s, 3H), 6.44 (s, 1H), 6.92-7.79 (m, 4H Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 14.32 (CH$_3$), 54.46 (CH$_3$), 55.21 (CH$_3$), 107.50 (CH), 113.92 (CH), 124.26 (C), 127.69 (CH), 145.50 (C), 151.05 (C), 154.00 (C), 160.27 (C); MS : m/z 246 (M$^+$, 100). Anal. Calcd for C$_{13}$H$_{14}$N$_2$O$_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.51; H, 5.70; N, 11.36.

Methyl 5-methyl-3-phenylpyrazole-1-carboxylate (16d)

96% mp 60-61°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.62 (s, 3H), 4.07 (s, 3H), 6.50 (s, 1H), 7.39 (m, 3H Ar), 7.83 (m, 2H Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 14.32 (CH$_3$), 54.52 (CH$_3$), 107.76 (CH), 126.37 (CH), 128.57 (CH), 129.00 (CH), 131.66 (C), 145.60 (C), 151.04 (C), 154.23 (C); MS : m/z 216 (M$^+$, 100). Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_2$: C, 66.66; H, 5.59; N, 12.95. Found: C, 66.58; H, 5.57; N, 13.00.

2,2-Dimethyl-5-(*N*´-methoxycarbonylhydrazino)-4-hexen-2-one (20).

Not isolated. Detected in the mixture by ^{1}H NMR. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ = 1.01 (s, 9H), 1.83 (s, 3H), 3.58 (s, 3H), 5.21 (s, 1H), 8.95 (br, NH), 11.35 (br, NH).

Preparation of 1-carboxamidepyrazoles from β-aminoenones. A solution of 18 mmol of the β-aminoenone and 20 mmol of **4** (as hydrochloryde) in 10 mL of water was stirred for the times given on the Tables 1, 2 and 3. At the end of the reaction, monitored by TLC, the solution is poured into water, and neutralized with saturated aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$, and the organic layer, dried (MgSO$_4$), and evaporated under reduced presure. The compounds (**6w, 15a, 15c, 15d, 18c, 18d, 24** and **25**) were thus obtained. The chemical yields and the physical spectral characteristics of these products are given below; **15b** and **18a** were detected by ^{1}H NMR in the reaction mixture.

3,5-Dimethylpyrazole-1-carboxamide (6w)

95%, mp 112-113°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.19 (s, 3H), 2.54 (s, 3H), 5.48 (br, NH), 5.90 (s, 1H) 7.26 (br, NH); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.59 (CH$_3$), 14.05 (CH$_2$), 110.09 (CH), 143.73 (C), 150.55 (C), 152.61 (C); MS : m/z 139 (M$^+$, 3), 96 (100). Anal. Calcd for C$_6$H$_9$N$_3$O: C, 51.78; H, 6.52; N, 30.20. Found : C, 51.63; H, 6.55; N, 30.31.

3-Methyl-5-(2-phenylethyl)pyrazole-1-carboxamide (15a)

97%, mp 114-115°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.21 (s, 3H), 2.94-3.00 (m, 2H), 3.28-3.33 (m, 2H), 5.32 (br, NH), 5.94 (s, 1H) 7.17-7.32 (m, 5H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.66 (CH$_3$), 24.53 (CH$_2$), 34.71 (CH$_2$), 109.34 (CH), 126.04 (CH), 128.38 (CH), 128.46 (CH), 141.13 (C), 147.61 (C), 150.58 (C), 152.19 (C); MS : m/z 229 (M$^+$, 78), 91 (100). Anal. Calcd for C$_{13}$H$_{15}$N$_3$O: C,

68.10; H, 6.59; N, 18.33. Found: C, 68.01; H, 6.62; N, 18.38.

5-*t*-Butyl-3-methylpyrazole-1-carboxamide (15b).

Not isolated. Detected in the mixture by ^{1}H NMR. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ = 1.21 (s, 9H), 2.13 (s, 3H), 3.35 (br, NH), 5.76 (s, 1H).

5-(4-Methoxyphenyl)-3-methylpyrazole-1-carboxamide (15c)

95%, mp 162-164°C from hexane-toluene. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ = 2.21 (s, 3H), 3.76 (s, 3H), 6.24 (s, 1H), 6.89-7.34 (m, 4H Ar) 7.49 (br, NH), 7.62(br, NH); ^{13}C NMR (75.4 MHz, DMSO-d$_6$) δ = 13.54 (CH$_3$), 55.14 (CH$_3$), 110.63 (CH), 113.00 (CH), 123.44 (C), 130.22 (CH), 145.30 (C), 149.15 (C), 151.24 (C), 159.17 (C); MS : m/z 272 (M$^+$, 4), 189 (100). Anal. Calcd for C$_{12}$H$_{13}$N$_3$O$_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.28; H, 5.64; N, 18.26.

3-Methyl-5-phenylpyrazole-1-carboxamide (15d)

91%, mp 115-116°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.30 (s, 3H), 5.15 (br, NH), 6.17 (s, 1H), 7.37-7.39 (m, 3H Ar), 8.14 (br, NH), 8.45-8.48 (m, 2H Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.62 (CH$_3$), 111.75 (CH), 127.63 (CH), 128.53 (CH), 129.11 (CH), 131.02 (C), 146.50 (C), 150.58 (C), 151.57 (C); MS : m/z 201 (M$^+$, 5), 158 (100). Anal. Calcd for C$_{11}$H$_{11}$N$_3$O: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.56; H, 5.53; N, 20.93.

5-Methyl-3-(2-phenylethyl)pyrazole-1-carboxamide (18a).

Not isolated. Detected in the mixture by ^{1}H NMR. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.54 (s, 3H), 2.82-3.05 (m, 2H), 3.26-3.29 (m, 2H), 5.32 (br, NH), 5.90 (s, 1H), 7.15 (br, NH), 7.20-7.33 (m, 5H Ar).

3-(4-Methoxyphenyl)-5-methylpyrazole-1-carboxamide (18c)

90%, mp 168-170°C from hexane-toluene. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ = 2.51 (s, 3H), 3.73 (s, 3H), 6.62 (s, 1H), 6.95-7.82 (m, 4H Ar and NH), 7.76 (br, NH); ^{13}C NMR (75.4 MHz, DMSO-d$_6$) δ = 13.98 (CH3), 55.16 (CH3), 106.35 (CH), 114.06 (CH), 124.52 (C), 127.21 (CH), 143.16 (C), 150.38 (C), 152.10 (C), 159.65 (C); MS : m/z 231 (M$^+$, 13), 188 (100). Anal. Calcd for C$_{12}$H$_{13}$N$_3$O$_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.32; H, 5.69; N, 18.13.

5-Methyl-3-phenylpyrazole-1-carboxamide (18d)

87%, mp 140-142°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 2.65 (s, 3H), 5.48 (br, NH), 6.45 (s, 1H), 7.31(br, NH), 7.36-7.88 (m, 5H Ar); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 14.21 (CH3), 107.16 (CH), 126.02 (CH), 128.64 (CH), 128.80 (CH), 131.93 (C), 144.35 (C), 152.15 (C), 152.36 (C); MS : m/z 201 (M$^+$, 28), 158 (100). Anal. Calcd for C$_{11}$H$_{11}$N$_3$O: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.56; H, 5.50; N, 20.98.

5-*i*-Propyl-3-methylpyrazole-1-carboxamide (24)

85%, mp 85-87°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 1.25 (d, J = 6.78, 6H), 2.21 (s, 3H), 3.78 (m, J = 6.78, 1H), 5.91 (br, NH,), 5.97 (s, 1H), 7.20 (br, NH); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 13.64 (CH$_3$), 22.50 (CH$_3$), 26.53 (CH), 106.00 (CH), 150.34 (C), 152.56 (C), 155.16 (C); MS : m/z 167

(M^+, 67), 109 (100). Anal. Calcd for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.13. Found: C, 57.53; H, 7.87; N, 25.01.

3-*i*-Propyl-5-methylpyrazole-1-carboxamide (25)

76%, mp 106-108°C from hexane-toluene. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 1.23 (d, J = 6.98, 6H), 2.56 (s, 3H), 2.88 (m, J = 6.98, 1H), 5.69 (br, NH,), 5.96 (s, 1H), 7.18 (br, NH); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ = 14.16 (CH$_3$), 22.10 (CH$_3$), 27.84 (CH), 107.29 (CH), 143.44 (C), 152.80 (C), 160.33 (C); MS : m/z 167 (M^+, 72), 109 (100). Anal. Calcd for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.13. Found: C, 57.52; H, 7.87; N, 25.07.

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\#   Dedicated to Prof. Joaquín De Pascual, In Memoriam.

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