Reactivity of *p*-Phenyl Substituted β-Enamino Compounds using K-10/ultrasound. I. Synthesis of Pyrazoles and Pyrazolinones

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The reactivity of the β-enamino ketones, 3-amino-1-(*p*-phenyl-substituted)-2-buten-1-ones **1a-d** and β-enamino esters. Ethyl-3-amino-3-(*p*-phenyl-substituted)-2-propenoates **5a-d** were evaluated by systematic studies of the reactions with hydrazine and methylhydrazine by reactions with solid support K-10/ultrasound and homogeneous media (reflux in ethanol or dichloromethane) yielding pyrazole rings **2a-d**, *N*-methylpyrazoles **3a-d**, **4a-d** and *N*-methylpyrazolinones **6a-c** and **7a-c**. The regiochemistry of the cyclization showed dependence of the reaction conditions employed as well as the substituent in the aromatic ring.

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Heterocyclic compounds such as pyrazoles and its derivatives continue to be a rich source of innovative chemistry because a number of pharmaceuticals and dyestuffs contain these ring systems [1]. The most important derivatives of pyrazole are pyrazolones which have significant pharmacological properties, although there are a few (naturally-occurring) examples. The standard syntheses for these compounds involve the reaction of β-dicarbonyl compounds with hydrazine [2]. The use of new bieletrophilic reagents for preparing pyrazoles and its derivatives have been studied [3-5].

β-Enamino ketones and esters have found application as 1,3-bieletrophilic synthons in syntheses of heterocycles [6,7]; different kinds of heterocycles may be formed depending on the reaction conditions employed.

We have been exploring the use of montmorillonite, K-10, as a solid support in the synthesis and reactivity of β-enamino compounds [8-10]. In order to study the reactivity of the eletrophilic center in the *p*-phenyl-substituted β-enamino ketones **1a-d** and esters **5a-d** we reacted these compounds with 1,2-dinucleophiles. We describe in this work the reaction of these compounds with hydrazine and methylhydrazine in heterogeneous media, K-10/ultrasound to obtain substituted pyrazoles and pyrazolinones.

The reaction of β-enamino ketones **1a-d** with hydrazine under K-10/ultrasound (method A) afforded pyrazoles **2a-d** (Scheme 1). We also tested this reaction under reflux in ethanol for 16 hours (method B) to obtain information on the media dependence of the regiochemistry of the pyrazole formed. In both media used (heterogeneous and homogeneous), the pyrazole formed showed the same spectral data (nmr ^1H and ^{13}C), but different melting points, indicating that probably different tautomeric mixtures were obtained. According to the ^1H nmr spectral data of the pyrazole **2a**, **b**, **d** (R^1 = H, Me, NO_2), the chemical shift of the nitrogen proton appear at 11-13 ppm, while for **2c** at 8.6 ppm. This observed variation can be attributed to a different isomeric form or the possibility of an intermolecular hydrogen bond.

The tautomerism of 5(3)-methyl-3(5)-phenylpyrazole was studied by Parrilla [11] in the liquid state using multinuclear nmr spectroscopy at low temperature and in the solid state by X-ray crystallography to determine the tautomeric equilibrium constants, they observed that the major tautomer in solution was the 5-methyl-3-phenylpyrazole tautomer whereas in the solid state both are present.

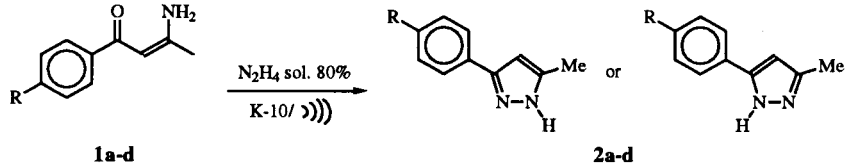
In view of this situation we decided to study the reaction of *p*-phenyl-substituted β-enamino compounds **1a-d** and **5a-d** with an unsymmetrical hydrazine.

The reaction of **1a** with methylhydrazine using K-10 as the solid support with ultrasound affords *N*-methyl-3-methyl-5-phenylpyrazole **3a** only, however for **1b-d** a regioisomeric mixture of pyrazoles **3,4b-d** result (see Scheme 2).

When β-enamino ketones **1a** and **1d** were treated with methylhydrazine in ethanol under reflux for 5 hours, the isomers **4a** and **4d** were isolated. But when an unsymmetrical hydrazine was condensed with **1b-c** in homogeneous media a regioisomeric mixture of **3,4b,c** result.

The ratio of the isomeric products **3** and **4** formed showed dependence of the reaction conditions used as well as the substituent on the aromatic ring.

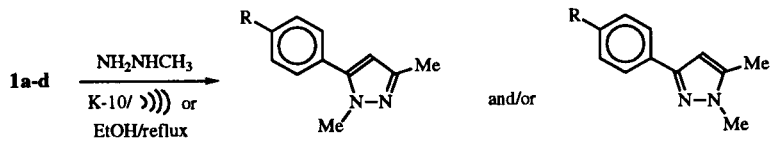
Scheme 1



1a-d **2a-d**

	a	b	c	d
R	H	Me	OMe	NO_2

Scheme 2



3a-d **4a-d**

Ratio of isomers **3,4a-d** [a]

	R	EtOH		K-10	
		3	4	3	4
a	H	–	100	100	–
b	Me	55	45	93	7
c	OMe	45	55	94	6
d	NO_2	–	100	20	80

[a] the ratio was determined by gas chromatography

These results showed the influence of the K-10 in the regiochemistry of these reactions. Presumably for steric reasons in the first step of this reaction, the interaction of K-10 with the nitrogen of the amino group makes the car-

Table

Selected Physical and Spectral [a] Data of Pyrazoles **2,3,4a-d** and *N*-Methylpyrazolinones **6a,c**

No.	Yield(%) [b] Method [c]		Mp [d] °C	Molecular Formula	Analysis (%) Calcd./Found			^{1}H-NMR δ, J (Hz)	^{13}C-NMR δ
	A	B			C	H	N		
2a	58		126-128	$C_{10}H_{10}N_2$ 158.20	75.92 75.78	6.37 6.35	17.71 17.69	2.09 (s, 3H, CH_3), 6.16 (s, 1H, CH), 7.12-7.63 (m, 5H, arom), 11.69 (s, 1H, NH)	11.5, 102.0, 125.8, 127.6, 128.6, 143.2, 149.9, 132.6.
2b	40		118-119	$C_{11}H_{12}N_2$ 172.23	76.71 76.59	7.02 7.04	16.27 16.15	2.16 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 6.21 (s, 1H, CH), 6.66-7.70 (m, 4H, arom), 11.74 (s, 1H, NH)	11.6, 21.0, 101.7, 125.6, 129.2, 129.2, 137.4, 143.5, 149.2
2c	70		70-73	$C_{11}H_{12}N_2O$ 188.23	70.19 69.96	6.43 6.35	14.88 14.80	2.18 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 6.17 (s, 1H, CH), 6.73-7.62 (m, 4H, arom), 8.60 (s, 1H, NH)	11.6, 55.1, 101.4, 101.4, 113.9, 125.2, 126.9, 143.5, 149.2, 159.3
2d	32		179	$C_{10}H_9N_3O$ 203.20	59.11 59.16	4.46 4.44	20.68 20.42	2.31 (s, 3H, CH_3), 6.60 (s, 1H, CH), 7.95-8.29 (m, 4H, arom), 12.99 (s, 1H, NH)	10.2, 102.2, 123.8, 125.5, 140.2, 146.0, 148.4, 150.3
3a	65	-	265	$C_{11}H_{12}N_2$ 172.23	76.71 76.59	7.02 7.08	16.27 16.11	2.27 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 6.05 (s, 1H, CH), 7.36 (s, 5H, arom)	13.1, 36.7, 105.3, 128.0, 128.4, 128.4, 130.7, 144.1, 147.3
3b	53	37	275	$C_{12}H_{14}N_2$ 186.26	77.37 77.21	7.58 7.37	15.05 14.94	2.27 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 6.02 (s, 1H, CH), 7.22 (s, 4H, arom)	13.1, 20.9, 36.7, 105.1, 127.8, 128.2, 129.0, 130.7, 144.2, 147.2
3c	60	43	73	$C_{11}H_{12}N_2O$ 202.26	71.26 71.30	6.98 7.10	13.85 13.62	2.27 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 6.01 (s, 1H, CH), 6.82-7.31 (m, 4H, arom)	13.2, 36.7, 55.1, 105.0, 113.8, 123.2, 129.7, 144.0, 147.2, 159.5
3d	8	-	191	$C_{11}H_{11}N_3O_2$ 217.23	60.82 60.69	5.10 5.11	19.34 19.01	2.33 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 6.45 (s, 1H, CH), 7.82-8.3 (m, 4H, arom)	11.1, 36.3, 103.5, 123.9, 125.6, 140.1, 140.4, 146.8, 147.5
4a	-	94	292	$C_{11}H_{12}N_2$ 172.23	76.71 76.50	7.02 7.10	16.27 16.18	2.17 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 6.24 (s, 1H, CH), 7.20-7.79 (2d, 5H, arom)	10.9, 35.8, 102.2, 125.2, 127.0, 128.3, 133.6, 139.5, 149.7
4b	4	30	95-97	$C_{12}H_{14}N_2$ 186.26	77.37 77.28	7.58 7.35	15.05 14.98	2.21 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 6.23 (s, 1H, CH), 7.09-7.68 (2d, 4H, arom)	11.0, 21.0, 37.8, 102.2, 125.2, 129.1, 131.0, 136.8, 139.5, 149.9
4c	4	52	91	$C_{11}H_{12}N_2O$ 202.26	71.26 71.14	6.98 6.93	13.85 13.61	2.21 (s, 3H, CH_3), 3.73 (s, 6H, CH_3), 6.19 (s, 1H, CH), 6.82-7.72 (2d, 4H, arom)	10.8, 35.6, 54.9, 101.7, 113.7, 126.3, 139.3, 139.3, 149.5, 158.9
4d	36	89	166	$C_{11}H_{11}N_3O_2$ 217.23	60.82 60.51	5.10 5.15	19.34 19.05	2.26 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 6.22 (s, 1H, CH), 6.82-7.72 (2d, 4H, arom)	12.3, 36.5, 105.8, 122.9, 128.2, 136.1, 141.0, 146.3, 146.7
6a	65	-	219-221	$C_{10}H_{10}N_2O$ 174.20	68.95 68.72	5.79 5.70	16.08 16.04	3.49 (s, 4H, CH_3), 7.22 (br, 7H, CH, NH and arom)	31.3, 100.3, 127.4, 127.9, 128.2, 131.1, 144.6, 157.8
6c		52	214-217	$C_{11}H_{12}N_2O_2$ 204.23	64.69 64.72	5.92 6.01	13.72 13.51	3.47 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 6.30 (br, 2H, NH and CH), 6.69-7.22 (m, 4H, arom)	31.6, 55.0, 100.3, 113.8, 124.3, 129.1, 144.9, 158.2, 159.1

[a] Spectra, nmr in deuteriochloroform/trimethylsilane (dimethyl-d_6 sulfoxide/trimethylsilane for **2d**), [b] Yields given for pure isolated products, [c] Methods: A: K-10/ultrasound; B: reflux in ethanol (dichloromethane for **7a** and **7c**), [d] Melting points were determined with a Microquímica APF-301 apparatus and are uncorrected.

boxylic carbon more electrophillic and the addition of the methylhydrazine occurs by initial addition of the unsubstituted nitrogen followed by cyclization to give the pyrazole **3**. However when **1d** was treated with methylhydrazine under K-10/ultrasound a mixture of **3** and **4** was isolated in a ratio 1:4 respectively, indicating that the regiochemistry was inverted. It can be attributed to a more effective interaction of K-10 with the nitro group than with the nitrogen or oxygen atoms of the enamino ketones and the reaction has a similar path to that of the reactions in homogeneous media.

In homogeneous media the reactivity of these systems is not affected by the steric hindrance in the first step and the formation of **4** is favored. For the β-enamino ketones bearing substituents Me for **1b** or OMe for **1c** on the aromatic ring, the reactivity changes and the steric hindrance is important. A mixture of the regioisomers **3** and **4** in a ratio of 1:1 results.

The synthesis of *N*-methyl-5(3)-methyl-3(5)-phenylpyrazole was described in the literature [12] by the reaction between benzoylacetone and methylhydrazine over alumina, the mixture of **3,4a** were isolated in the ratio of 2:3. In our case when K-10/ultrasound was employed the only isolated product was the pyrazolone **3a**, indicating the selectivity of K-10 in these reactions.

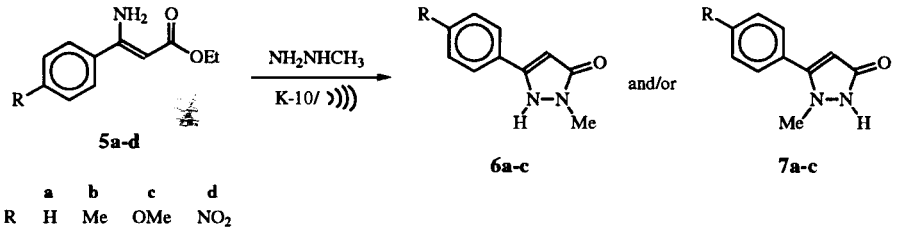
The structure of the pyrazoles **3a-d** and **4a-d** were confirmed by spectral data. The ^{1}H nmr spectra showed a significant difference in the chemical shifts. The appearance of the phenyl signal at position 3 (two multiplets, H_o and $H_m + H_p$) for **3** is very different from that of the phenyl at position 5 (a singlet due to the steric hindrance of NMe) for **4**, for example: **3a** 7.36 ppm (phenyl at position 5); **4a** 7.20-7.79 ppm (phenyl at position 3). Similar variations were observed in the ^{13}C nmr data (see Table).

however in homogeneous media, reflux in dichloromethane for 20 hours the mixture of **6a** and **7a** was isolated. This was observed by ^{1}H nmr spectra where the methyl protons of the N-Me group exhibit different chemical shifts and give two separate signal at and 3.49 ppm and 2.60 ppm corresponding of the pyrazolinones **6a** and **7a** respectively. In the ^{13}C nmr spectra, the carbon of the N-methyl group appears at 31.3 ppm for the pyrazolinone **6a** and 36.9 ppm for pyrazolinone **7a**; this was confirmed by a DEPT 135 experiment. The cyclization of **5b** with methylhydrazine results in a mixture of **6b** and **7b** independent of the media employed. For ethyl 3-amino-3-(*p*-methoxyphenyl)-2-propenoate **5c**, the cyclization with methylhydrazine under K-10/ultrasound results in a mixture of **6c** and **7c**, but the same reaction under reflux in dichloromethane gives **6c** only. The pyrazolinones **6,7b** were not separated from the mixture. The structures of **6a-c** compounds were established based on the ^{1}H and ^{13}C nmr spectra which show different chemical shifts (see Experimental).

When the ethyl 3-amino-3-(*p*-nitrophenyl)-2-propenoate **5d** was treated with methylhydrazine the reaction did not take place, only starting material was isolated from the reaction, independent of the conditions employed (K-10/ultrasound or reflux in dichloromethane). This is probably due to the influence of the aromatic ring bonded directly on the α,β-unsaturated system.

For the results described here we conclude that β-enamino ketones **1a-d** are more reactive than β-enamino esters **5a-d** in the cyclization proposed. The regiochemistry of the cyclization showed dependence of the reaction conditions employed as well as the substituent in the aromatic ring. The influence of K-10 was demonstrate in the regiochemistry of the products obtained as well in compounds that have polar groups due the interactions substrate/support.

Scheme 3



The reaction of β-enamino esters, 3-amino-3-(*p*-phenyl-substituted) ethyl 2-propenoate **5a-d** with methylhydrazine to afford pyrazolinones (Scheme 3) was performed using the same methodology used for β-enamino ketones in order to evaluate the effect of the K-10/ultrasound and the substitution of the *p*-substituted-phenyl group at position 3 in the regiochemistry of this reaction.

The reaction of **5a** with methylhydrazine under K-10/ultrasound for 6 hours gave the pyrazolinone **6a** only,

EXPERIMENTAL

Melting points were determined with a Microquímica APF-301 apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AC-80 and Varian XL-200 spectrometers in deuteriochloroform/trimethylsilane or dimethyl-d_6 sulfoxide/trimethylsilane. Elemental analyses were carried out on a Vario CHN-standard analyser. Capillary gc analyses were performed on a Carlo Erba, Mega Series 5400 chromatograph

equipped with a split/splitless injector and a FID detector. A ultrasound bath (water), Thornton, 50-60 Hz, 110/220 volts, 1.0 Amps was used, the water bath was maintained at rt β-Enamino compounds **1** and **5** were prepared according to the know procedure [10].

5(3)-Methyl-3(5)-(*p*-phenyl-substituted)-1*H*-pyrazoles **2a-d**.

General Procedure.

Hydrazine hydrate (80%) (4 mmoles) in dichloromethane (1 ml) was added dropwise to the 1-(*p*-phenyl-substituted)-3-amino-2-buten-1-one **1a-d** (2 mmoles) dispersed on montmorillonite K10 (0.6 g, Fluka); the mixture was placed in the ultrasound bath for 5 hours. The products were extracted by washing the montmorillonite with dichloromethane, the organic layer was washed with water, dried over magnesium sulfate, filtered and the solvent was removed *in vacuo* to yield the crude products. Compounds **2a**, **2b** and **2c** were purified by recrystallization from petroleum ether/diisopropyl ether 10% and **2d** was recrystallized from ethanol to give **2a** (58%), **2b** (40%), **2c** (70%) and **2d** (42%).

1,3-Dimethyl-5-(*p*-substituted-phenyl)pyrazoles **3a-d**, 1,5-Dimethyl-3-(*p*-substituted-phenyl)pyrazoles **4a-d** and 3(5)-(*p*-Phenyl-substituted)-*N*-methyl-5(3)-pyrazolinones **6,7a-c**.

General Procedure. Method A.

Methyl hydrazine (3 mmoles) in dichloromethane (1 ml) was added dropwise to the 1-(*p*-phenyl-substituted)-3-amino-2-buten-1-ones **1a-d** or ethyl 3-amino-3-(*p*-phenyl-substituted)-2-propenoate (1 mmole) **5a-c** dispersed on montmorillonite K10 (0.3 g, Fluka). The mixture was placed under an ultrasound bath for 6 hours, extracted by washing the montmorillonite with dichloromethane and the solvent was evaporated in a rotary evaporator under vacuum. The crystals were dissolved in dichloromethane and the organic layer was washed with water, dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*, to yield **3a** (65%) and a mixture of **3,4 b-d**. The mixtures were separated by column chromatography on silica gel (Aldrich, 230-400 mesh), using dichloromethane as eluent resulting **3b** (53%), **4b** (4%), **3c** (60%), **4c** (4%), **3d** (8%) and **4d** (36%). The isomeric mixture of **6,7b** (78%), **6,7c** (78%) were obtained and **6a** in 65% yield.

Method B.

Methylhydrazine (3 mmoles) was added dropwise to a stirred solution of the 1-(*p*-phenyl-substituted)-3-amino-2-buten-1-ones **1a-d** or ethyl 3-amino-3-(*p*-phenyl-substituted)-2-propenoates **5a-c** (1 mmole) in ethanol (15 ml). The mixture was stirred and refluxed for 5 hours. The solvent was evaporated in a rotary evaporator under vacuum, the crystals were dissolved with dichloromethane and the organic layer was washed with water, dried over magnesium sulfate, filtered and the solvent was removed *in vacuo*, resulting in **4a** (94%) and **4d** (89%). The mixtures **3,4b** and of **3,4c** were applied to a silica gel (Aldrich, 230-400 mesh) column and eluated with dichloromethane to give **3b** (37%), **4b** (30%), **3c** (43%), **4c** (52%). The isomeric mixtures of **6,7a** (62%), **6,7b** (72%) were obtained and also **6c** in 52% yield.

Compound **6b**.

This compound had ^{1}H nmr (deuteriochloroform): δ = 2.32 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 4.00 (br, 1H, NH), 7.01-7.12 (s, 5H, CH and arom); ^{13}C nmr (deuteriochloroform): δ = 31.7, 20.8, 100.7, 124.0, 127.8, 113.9, 129.1, 144.6, 158.2 ppm.

Compound **7a**.

This compound had ^{1}H nmr (deuteriochloroform): δ = 2.60 (s, 3H, CH_3), 7.19 (br, 7H, NH, CH and arom); ^{13}C nmr (deuteriochloroform): δ = 36.9, 99.2, 127.6, 128.1, 133.7, 145.1, 157.9 ppm.

Compound **7b**.

This compound had ^{1}H nmr (deuteriochloroform): δ = 2.32 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.00 (br, H, NH); 7.01-7.12 (s, 5H, CH and arom); ^{13}C nmr (deuteriochloroform): δ = 36.9, 20.8, 100.7, 124.1, 127.8, 113.9, 129.1, 144.6, 158.2 ppm.

Compound **7c**.

This compound had ^{1}H (deuteriochloroform): δ = 2.63 (s, 3H, CH_3); 3.76 (s, 3H, CH_3); 6.70-7.23 (6H, m, CH, NH and arom); ^{13}C nmr (deuteriochloroform): δ = 37.0, 55.0, 100.4, 113.9, 124.0, 129.2, 144.9, 158.2, 159.2 ppm.

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