Reactivity of *p*-Phenyl Substituted β-Enamino Compounds using K-10/ultrasound. **II** [1]. Synthesis of Isoxazoles and 5-Isoxazolones

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The condensation of 4-phenyl substituted β-enamino ketones **1a-d** and β-enamino esters **5a-d** with hydroxylamine hydrochloride using K-10 as the solid support under sonication was studied to evaluate the formation of isoxazole and 5-isoxazolone rings from β-enamino compounds with a substituted aromatic ring. Isoxazoles **2a-c**, **3c-d** and 5-isoxazolones **6a-c** and **7a-d** were obtained. The use of K-10/ultrasound in this reaction furnished novel results in some cases.

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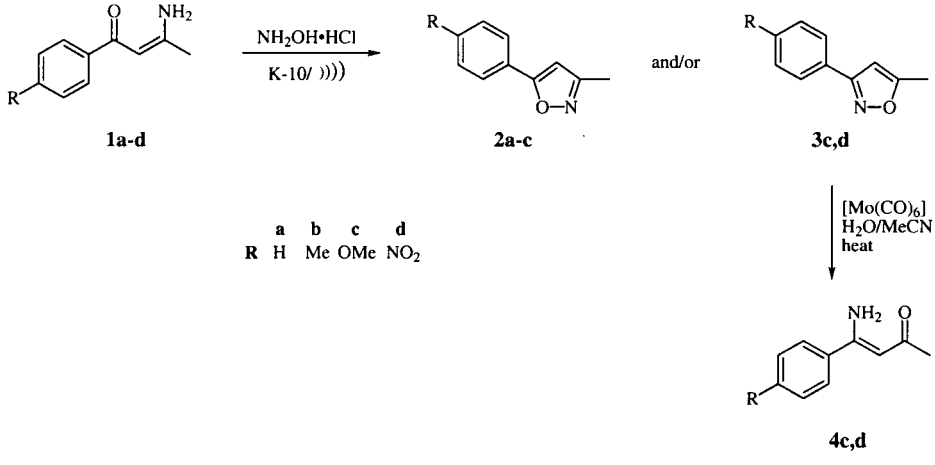
Scheme 1



1a-d **2a-c** **3c,d** **4c,d**

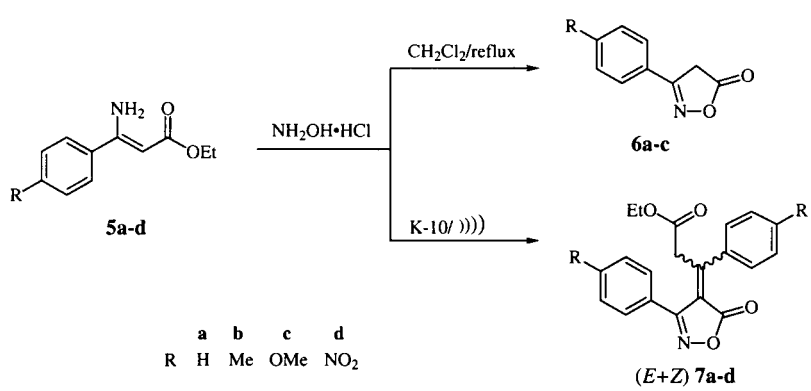
Introduction.

We have been interested in the synthesis of heterocycles such as pyrazoles [1-2], isoxazoles and its derivatives from β-enamino compounds as starting materials, using montmorillonite K-10 as solid support [3-5].

Much interest has been given to the 3-substituted isoxazole moiety, which is found in a variety of physiologically active compounds [6-8] which show muscle relaxant and anticonvulsant activities.

In this work the 3-(5)-methyl-5(3)-(4-phenyl substituted)-isoxazoles **2a-c, 3c,d,** 3-(4-phenyl-substituted)-4,5-dihydro-5-isoxazolone **6a-c** and ethyl 3-[(4-phenyl-substituted)-5-oxo-4,5-dihydro-4-isoxazolyliden]-3-(4-phenyl-substituted)propanoates **7a-d** were obtained by the ring closure of β-enamino ketones **1a-d** and β-enamino esters **5a-d** with hydroxylamine hydrochloride using montmorillonite (K-10), as the solid support under sonication. This methodology was previously

Scheme 2



5a-d **6a-c** (*E*+*Z*) **7a-d**

Table 1

Selected Physical and Spectral [a] Data for Isoxazoles **2a-c**, **3d** and 5-Isoxazolones **6a-c**,**7a-d**

No.	Yield [c] (%)	Mp [d] °C	Molecular Formula	Analysis(%) Calcd./Found C	H	N	^{1}H-NMR [e] δ, J(Hz)	^{13}C-NMR [e] δ
2a	91	66	$C_{10}H_9NO$ 159.19	75.45 75.37	5.70 5.73	8.80 8.77	2.31 (s, 3H, CH_3), 6.31 (s, 1H, CH), 7.35-7.74 (m, 5H, arom)	11.4, 100.1, 125.7, 127.6, 128.8, 129.9, 160.2, 169.6
2b	94	86	$C_{11}H_{11}NO$ 173.21	76.28 76.08	6.40 6.45	8.09 8.01	2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.27 (s, 1 H, CH), 7.16-7.66 (m, 4H, arom)	11.2, 21.1, 99.4, 124.7, 125.4, 129.3, 139.9, 160.0, 169.6
2c	89	110	$C_{11}H_{11}NO_2$ 189.21	69.83 69.81	5.86 5.85	7.40 7.36	2.31 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.21 (s, 1H, CH), 6.88-7.72 (m,4H, arom)	11.2, 55.1, 114.2, 98.6, 120.3, 127.1, 160.0, 160.8, 169.4
3d	99	186	$C_{10}H_8N_2O_3$ 204.19	58.82 58.78	3.95 3.75	13.72 13.68	2.39 (s, 3H, CH_3), 6.55 (s, 1H, CH), 7.85-8.37 (m, 4H, arom)	11.4, 102.8, 124.3, 126.4, 132.9, 160.7, 167.1
6a [b]	58	149-151	$C_9H_7NO_2$ 161.16	67.10 66.84	4.40 4.46	8.70 8.73	3.84 (br, 2H, CH_2), 7.40-7.64 (m, 5H, arom)	33.8, 126.2, 128.7, 130.9, 131.7, 163.1, 174.6
6b	64	131-133	$C_{10}H_9NO_2$ 175.19	68.56 68.37	5.18 4.91	8.00 7.87	2.39 (s, 3H, CH_3Ph), 3.71 (s, 2H, CH_3), 7.24 (d, 2H arom, J = 8.2), 7.53 (d, 2H, arom, J = 8.2)	21.5, 33.9, 124.8, 126.5, 129.8, 142.7, 163.1, 174.9
6c [b]	75	134-136	$C_{10}H_9NO_3$ 191.19	62.82 62.51	4.74 4.85	7.33 7.06	3.81 (s, 3H, CH_3), 3.82 and 3.90 (s, 2H, CH_2), 6.96 (d, 2H arom, J = 8.4), 7.61 (d, 2H arom, J = 8.4)	33.0, 54.0, 113.1, 118.9, 127.0, 160.8, 162.2, 174.4
7a	64	93-95	$C_{20}H_{17}NO_4$ 335.36	71.63 71.58	5.11 5.15	4.18 4.02	1.20 (t, 3H, CH_3, J = 7.1), 3.78 {3.82} {s, 2H, CH_2}, 4.11 (q, 2H, CH_2, J = 7.1), 7.25-7.73 (m, 8H, arom)	{13.9}, 18.1, {32.8}, 33.9, {58.2}, 61.1, 126.1, 126.5, 127.5, 128.4 {129.1}, 129.3, 132.0, 135.4, 152.3, 163.2, 169.0, 174.9
7b	80	129	$C_{22}H_{21}NO_4$ 363.41	72.71 72.54	5.82 5.91	3.85 3.78	1.94 (t, 3H, CH_3, J = 7.1), 2.33 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.73, {3.80} (s, 2H, CH_2), 4.10 (q, 2H, CH_2, J = 7.1), 7.08-7.56 (8H, m, arom)	{14.0}, 18.2, 21.2, 21.5, {32.7}, 34.0, {58.3}, 61.2, 124.7, 126.0, 126.5, 128.6, 129.2, 129.8, 132.4, 139.4, 142.7, 152.3, 163.1, 169.0, 175.1
7c	56	143-145	$C_{20}H_{21}NO_6$ 395.41	66.83 66.71	5.35 5.45	3.54 3.68	1.99 (t, 3H, CH_3, J = 7.1), 3.79 {3.83} (s, 2H, CH_2), 3.83 (s, 3H, CH_3), 4.10 (q, 2H, CH_2), 6.88-7.95 (8H, m, arom)	13.4, {31.9}, 33.4, 54.8, {60.4}, 60.7, {113.0}, 113.3, 113.9, 119.4, 126.9-130.2, 151.4, 161.9, 162.8, 172.0, 174.3
7d	60	86	$C_{20}H_{15}N_3O_8$ 425.35	56.48 56.37	3.55 3.71	9.88 9.75	1.23 (t, 3H, CH_3, J = 7.6), 3.64 {3.87} (s, 2H, CH_2), 4.18 (q, 2H, CH_2, J = 7.6), 7.73-8.28 (m, 8H, m, arom)	{13.9}, 18.0, {32.2}, 33.7, {58.3}, 61.5, 117.7, 123.7, 126.9, 141.4, 148.2, 150.9, 165.6, 168.4

Spectra, nmr in [a] deuteriochloroform/tetratmethylsilane, [b] dimethyl-d_6 sulfoxide/tetramethylsilane. [c] Yields given for pure isolated products. [d] Melting points were determined with Microquímica APF-301 apparatus and are uncorrected. [e] In braces duplicated signs (*E/Z*).

described by the authors for use in reactions to obtain pyrazoles and pyrazolinones [1].

The condensation of β-enamino ketones **1a-d** with hydroxylamine can produce two types of isoxazoles: 3-methyl-5-phenylisoxazole **2** and 5-methyl-3-phenylisoxazole **3** (Scheme 1). To determine the regiochemistry of the isoxazoles formed, we promoted the thermally induced reductive cleavage of N-O bond with $[Mo(CO)_6]$ to give corresponding starting β-enamino ketones. This reaction involves an *N*-complexed isoxazole pentacarbonyl-molybdenum intermediate [9], a convenient method for the characterization of the starting β-enamino ketones.

The isoxazoles **2a** and **2b** were the only products isolated from **1a** and **b** after the reaction of **1a-d** with hydroxylamine hydrochloride under K-10/ultrasound for 3 hours (Scheme 1). Under the same conditions, **1c** gives a mixture of **2c** and **3c** in the ratio of 1.1:1.0 and the reaction of **1d** yields **3d** only. This was confirmed when the mixture of **2,3c** and the isoxazole **3d** were submitted a thermally induced reductive cleavage of the N-O bond in the presence of $[Mo(CO)_6]$ and water to give the β-enamino ketones **4c** and **4d**, while the same reaction with **2a** and **2b** gives the β-enamino ketones **1a** and **1b** respectively.

The structures of the β-enamino ketones obtained by isoxazole ring-opening were confirmed by nmr spectral data, ^1H and ^{13}C in comparison with known β-enamino ketones **1a-d** previously reported [5], the nmr data of β-enamino ketones **4c** and **4d** are described in the Experimental.

When ethyl 3-amino-3-(4-phenyl-substituted) 2-propenoates **5a-d** were allowed to react with hydroxylamine hydrochloride in dichloromethane under reflux for 20 hours, the expected 3-(4-phenyl-substituted)-4,5-dihydro-5-isoxazolones **6a-c** were formed. Ethyl 3-amino-3-(4-nitrophenyl)-2-propenoate **5d** does not react under these conditions, only starting materials were isolated from the reaction. However when the same reaction was performed using K-10/ultrasound, ethyl 3-(5-oxo-3-[3-(4-phenylsubstituted)-4,5-dihydro-4-isoxazolyliden]-3-(4-phenyl-substituted)propanoates **7a-d** were isolated as a mixture of *E*- and *Z*-isomers (Scheme 2).

The proposed structure of 5-oxoisoxazolylidene **7** obtained agrees completely with its ^1H and ^{13}C nmr spectral data. The existence of an isomeric mixture (*E/Z*) was confirmed by duplicate signals (see spectral data, Table 1) and by gc/ms for **7b** where two peaks at m/z 363 each, corresponding to stereoisomers *E* and *Z*, were observed. The relative proportion of isomers have been established on basis of ^1H nmr, resulting in a ratio (*E* to *Z*) of 1:3 for **7a,7c** and **7d** and 1:1.1 for **7b**.

The formation of 5-oxoisoxazolylidene **7** in "one pot" was unexpected, it can be considered to proceed by the initial formation of **6** followed by condensation with a second molecule of the β-enamino ester. Probably it was favored by the catalytic properties of K-10. These compounds are quite rare, and as far as we know, no general method for their preparation has been reported to date.

EXPERIMENTAL

Melting points were determined with a Microquímica APF-301 apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AC-80 and a Bruker DPX-200 spectrometer in deuteriochloroform/tetramethylsilane or dimethyl-d_6 sulfoxide/tetramethylsilane. 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 FID detector. An 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 by the procedure previously described [5].

3-(5)-Methyl-5(3)-(4-phenyl-substituted)-isoxazoles **2a-c, 3c,d** and Ethyl 3-[(4-Phenyl-substituted)-5-oxo-4,5-dihydro-4-isoxazolyliden]-3-(4-phenyl-substituted) Propanoates **7a-d**.

General Procedure.

Hydroxylamine hydrochloride (2 mmoles) in dichloromethane (1 ml) was added dropwise to the 3-amino-1-(4-phenyl-substituted)-2-buten-1-ones **1a-d** or 3-amine-1-(4-phenyl-substituted)-ethyl 2-propenoates **5a-d** (1 mmole) dispersed on montmorillonite K10 (0.3 g, Fluka), the mixture was placed in an ultrasound bath for 3 hours (6 hours for **5a-d**). The products were extracted by washing the montmorillonite with dichloromethane, then the organic layer was washed with water (3 x 10 ml), dried over magnesium sulfate, filtered and the solvent was removed *in vacuo* to yield the crude products. They were purified by recrystallization from ethanol to give: **2a** (91%), **2b** (94%) a mixture of **2,3c** (89%) and **3d** (99%); compounds **7a-d** were purified by recrystallization from dichloromethane/petroleum ether, yields for **7a** (64%), **7b** (80%), **7c** (56%) and **7d** (60%).

Thermal Reactions of Isoxazoles **2** and **3**.

Following the general procedure [8] a solution of the isoxazole (1 mmole), water (1 mmole) and $[Mo(CO)_6]$ (1.2 mmoles) in acetonitrile (20 ml) was refluxed for 20 hours. The reaction mixture was filtered through celite, the filtrate was concentrated by rotatory evaporation to give β-enamino ketones **1a-c**, **4c** and **4d**.

Compound **4c** had ^1H nmr (80 MHz, deuteriochloroform): δ = 2.13 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 5.25 (s, 1H, CH), 6.81-7.88 (m, 4H, arom), 10.00 (br, 2H, NH_2); ^{13}C nmr (20 MHz, deuteriochloroform): δ = 25.1, 55.4, 95.7, 113.8, 128.9, 132.9, 162.5, 163.0, 183.9.

Compound **4d** had ^1H nmr (80 MHz, deuteriochloroform): δ = 2.43 (s, 3H, CH_3), 4.93 (br, 2H, NH_2), 5.39 (s, 1H, CH), 6.56-7.75 (4H, m, arom); ^{13}C nmr (20 MHz, deuteriochloroform $_3$): δ = 25.1, 95.8, 122.3, 126.7, 144.5, 147.3, 182.6, 195.0.

3-(4-Phenyl-substituted)-4,5-dihydro-5-isoxazolones **6a-c**.

3-Amine 3-(4-phenyl-substituted)ethyl 2-propenoates **5a-d** (1 mmole) were mixed with hydroxylamine hydrochloride (2 mmoles) in dichloromethane. The mixture was refluxed for 20 hours, washed with and distilled water (3 x 10 ml). The organic

layer was dried over magnesium sulfate, filtered and the solvent was evaporated by rotatory evaporation to give **6a** (58%), **6b** (64%), **6c** (75%). The compounds were purified by recrystallization from dichloromethane/petroleum ether.

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