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Three-Component Synthesis of Enaminones Based on Homoveratrilamine and Aromatic Aldehydes

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Abstract: An efficient one-reactor procedure leading to β-enaminones has been developed. The developed methodology involves a multicomponent [1+2+1] cyclocondensation reaction of starting materials. As starting materials we used homoveratrilamine as the primary amine source and acetoacetic ether as the dicarbonyl compound and a number of aromatic aldehydes. Mild reaction conditions, simple and rapid methods of purification and separation of the obtained products further facilitated the synthesis process. The structure of the synthesized substances was established by IR, ^{1}H and ^{13}C NMR spectra and physical constants were studied.

Keywords: three-component [1+2+1] synthesis, enaminone, and acetoacetic ester, homoveratrilamine.

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Introduction

Enaminones and some of its derivatives are the most common compounds associated in the structures of most pharmaceuticals [1]. Recently, much interest has been devoted to the synthesis of cyclic enaminones due to their diverse therapeutic and pharmacological properties. Various enaminone derivatives are characterized by moderate toxicity and are central nervous system stimulants [2] and have anti-inflammatory activity [3].

They are also attractive substrates for the synthesis of various heterocyclic compounds [4-6]. Enaminones can be obtained by the nucleophilic addition of

secondary amines to 1,2,3-triazine [7] or by the amination of 1,3-dicarbonyl compounds with primary amines or ammonium salts [8,9]. In addition, these compounds can be prepared through the reaction of α-keto acids with iodoalkyne [10] and oxyaminalization of alkenes using amines, oxygen and Togni's reagent [11]. Iron catalyzed synthesis has also been reported using ketones and amines [12].

The goal is, as a continuation of our previous work [13], the present study carried out reactions for the preparation of enaminone derivatives in the presence of homoveratrilamine , acetoacetic ester and various aromatic aldehydes according to the [1+2+1] one-pot synthesis scheme and the establishment of their structure.

Materials and methods: IR spectra were recorded on an FTIR system 2000 instrument (Perkin-Elmer, USA) in tablets with KBr; ^{1}H and ^{13}C NMR spectra were recorded on JNM-ECZ600R spectrometers (JEOL, Japan) ($CDCl_3$ solvents, solvent signal for chemical shifts ^{1}H NMR internal standard - TMS (δ 0.00 ppm) and for chemical shifts ^{13}C NMR ($CDCl_3$ - 77.16 ppm)). The *Rf* value was determined by TLC in silyfol L/W (10x20 cm) with 254 nm fluorescent indicators (Sigma-Aldrich, Germany) using elution systems C_6H_6:CH_3OH (6:1). Developers: iodine vapor, UV light, Dragendoroff reagent . The melting points of all synthesized substances were determined on a Stuart SMP20 digital instrument with an accuracy of ±0.1°C.

General method for the synthesis of enaminones

To a solution of 1.0 mmol of aromatic aldehyde and 1.0 mmol of homoveratrilamine in 10 ml of ethanol was added 2.0 mmol of acetoacetic ester. The mixture was stirred for 3-7 days. The progress of the reaction was monitored by TLC. The solvent was removed at room temperature by slow evaporation. The resulting reaction mixture was washed with a small amount of cooled ethanol (5-7°C) on a filter. The remaining powder of the target product was analyzed by NMR spectroscopy.

Synthesis of 5- N -((3,4- dimethoxyphenylethyl) amino)-2,4-diethylether-1-methyl-3- *p* -dimethylaminophenylcyclohexen-4-ol-1, $C_{31}H_{42}N_2O_7$

Received from 0.4 g (0.39 ml, 1.0254 g/ml, 2.5 mmol) *p*-dimethylaminobenzaldehyde , 0.68 g (0.66 ml, ϱ=1.0284 g/ml, 5.0 mmol) acetoacetic ester, 0.47 g (0.44 ml, ϱ=1.074 g/ml , 2.5 mmol) homoveratrilamine for 10 days. Yield 1.13 g (82.5%), oily (chloroform), R_f 0.73 (benzol-methanol, 8:1).

Synthesis of 5-N-((3,4- dimethoxyphenylethyl) amino)-2,4-diethyl ether-1-methyl-3-*p*-methoxyphenyl-cycohexene-4-ol-1, $C_{30}H_{39}NO_8$

Received from 0.385 g (0.34 ml, 1.119 g/ml, 2.8 mmol) *p*- methoxybenzaldehyde, 0.74 g (0.72 ml, ϱ=1.0284 g/ml, 5.6 mmol) acetoacetic ester, 0.51 g (0.47 ml, ϱ=1.074 g/ml, 2.8 mmol) homoveratrilamine for 10 days. Yield 1.27 g (85%), oily (chloroform), R_f 0.6 (benzol-methanol, 6:1).

^{1}H NMR spectrum: (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.08 (3H, t, J=7.1, Et-CH_3), 1.23 (3H, t, J=7.1, Et-CH_3), 1.83 (3H, s, CH_3 -1'), 2.04 (1H, d, J=10.1, H-6'a); 2.31 (1H, d, J=10.5, H-6'e)), 2.81 (2H, m, H- α), 3.07 (1H, d, J=1.4, H-2'), 3.49 (2H, kv , J=7.1, H-β), 3.75 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.86 (1H, d , J=2.3, H-3'), 3.98 (2H, kv, J=7.1, Et-CH_2), 4.15 (2H, kv, J=7.1, Et-CH_2), 6.18 (1H, d, OH), 6.69 (1H, d, J=8.8, ArH-5), 6.73 (2H, dd , J=2.2, 8.9, ArH-2, 6), 6.99 (1H, d, J=8.8, H-2'), 7.09 (2H, dt, J= 2.3 , 8.8, ArH-3', 5'), 7.18 (1H, d, J=8.8, ArH- 6'), 8.96 (1H, wide.s., NH).

^{13}C NMR spectrum: (100 MHz , $CDCl_3$, δ, ppm): 14.04 (Et-CH_3), 14.24 (Et-CH_3), 21.97 (CH_3 -1'), 29.78 (C- β), 34.91 (C-6 '), 35.06 (C-3'), 41.22 (C- α), 46.31 (C-2'),

55.05 (OCH_3), 55.87 (OCH_3), 56.00 (CH_3), 61.12 (Et-CH_2), 62.29 (Et-CH_2), 111.46 (C-1'), 111.85 (C-4'), 112.32 (C-2), 115.63 (C-5), 117.65 (C-5''), 120.75 (C-3''), 127.42 (C-6), 127.53 (C-6''), 128.39 (C-2''), 128.80 (C-1), 129.13 (C-1''), 155.66 (C-4) , 157.18 (C-3), 168.91 (C-5'), 170.91 (C-4''), 192.63 (C=O), 194.13 (C=O).

Synthesis of 5-N-((3,4-dimethoxyphenylethyl)amino)-2,4-diethylether-1-methyl-3-*p*-hydroxyphenylcyclohexen-4-ol-1, $C_{29}H_{37}NO_8$

Received from 0.27 g (0.22 ml, 1.226 g/ml, 2.0 mmol) *p*-hydroxybenzaldehyde, 0.57 g (0.56 ml, ϱ=1.0284 g/ml, 4.0 mmol) acetoacetic ester, 0.4 g (0.37 ml, ϱ=1.074 g/ml, 2.0 mmol) homoveratrilamine for 10 days. Yield 0.83 g (79%), in the form of a powder, Tm.p. 168-171°C, *Rf* 0.81 (benzol-methanol, 4:1).

^{1}H NMR spectrum: (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.17 (3H, t, J=7.1, Et-CH_3), 1.36 (3H, t, J=7.1, Et- CH_3), 2.30 (3H, s, CH_3-1'), 2.75 (1H, m, H-6'a), 2.78 (2H, t, J=7.1, H-α), 2.92 (1H, d , J=7.1, H-6'e), 3.48 (1H, d, J=7.0, H-2'), 3.52 (2H, q, J=7.1, H-β), 3.75 (1H, s, OH), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.87 (1H, d, J=2.2, H-3'), 4.25 (2H, q , J=7.1, Et- CH_2), 4.29 (2H, kv, J=7.1, Et-CH_2), 4.47 (1H, s, OH), 6.67 (1H , d, J=2.0, ArH-2), 6.69 (2H, dd , J=2.1, 7.3, ArH-5, 6), 6.71-6.74 (4H, m, ArH-2'', 3'', 5'', 6'').

^{13}C NMR spectrum: (100 MHz , $CDCl_3$, δ, ppm): 10.91 (Et-CH_3), 14.34 (Et-CH_3), 14.37 (CH_3 -1'), 15.26 (C- β), 35.12 (C- 6'), 36.61 (C-3'), 41.04 (C- α), 46.12 (C-2'), 56.00 (2 OCH_3), 60.17 (Et-CH_2), 60.61 (Et-CH_2), 61.29 (C-1', 4'), 65.01 (C-2, 5), 96.20 (C-5'', 3''), 111.49 (C-6), 111.84 (C-2'', 6''), 112.00 (C-1''), 120.72 (C-4), 120.84 (C-3), 130.39 (C-5'), 130.65 (C-4''), 149.16 (2 C=O).

Synthesis of 5-N-((3,4-dimethoxyphenylethyl)amino)-2,4-diethylether-1-methyl-3-*o*-methoxyphenylcyclohexen-4-ol-1, $C_{27}H_{32}NO_5$

Received from 0.25 g (0.22 ml, 1.127 g/ml, 1.8 mmol) *o*- metoxybenzaldehyde, 0.47 g (0.46 ml, ϱ=1.0284 g/ml, 3.6 mmol) acetoacetic ester, 0.332 g (0.3 ml, ϱ=1.074 g/ ml, 1.8 mmol) homoveratrilamine for 10 days. Yield 0.77 g (80.5%), in the form of a powder, m.p. 155-157°C, *Rf* 0.8 (benzol-methanol, 6:1).

^{1}H NMR spectrum: (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.01 (3H, t, J=7.0, Et-CH_3), 1.23 (3H, t, J=7.1, Et- CH_3), 1.77 (3H, s, CH_3 -1'), 2.03 (1H, d, J=8.6, H-6'a); 2.24 (1H, d, J=7.3, H-6'e)), 2.81 (2H, m, H-α), 3.16 (1H, d, J=1.4, H-2'), 3.51 (2H, m, H-β), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.89 (1H, d, J=3.7, H-3'), 4.12 (2H, m , Et-CH_2) , 4.18 (2H, m, Et-CH_2) , 6.15 (1H, wide.s., OH), 6.74-6.78 (3H , m, ArH-2,5,6), 6.82 (1H, dd , J=1.2, 8.1, ArH-3''), 6.91 (1H, dd , J=2.4, 7.6, ArH-6''), 7.12 (1H, dt, J = 1.8 , 8.0, ArH-4''), 7.22 (1H, dt, J=2.4, 8.1, ArH-5'') , 9.01 (1H, wide.s., NH).

^{13}C NMR spectrum: (100 MHz , $CDCl_3$, δ, ppm): 14.26 (Et-CH_3), 14.50 (Et-CH_3), 24.81 (CH_3 -1'), 33.05 (C- β), 37.02 (C-6'), 45.03 (C-3'), 50.49 (C- α), 52.34 (C-2'), 55.62 (OCH_3), 55.89 (OCH_3), 55.99 (OCH_3), 58.61 (Et-CH_2), 60.84 (Et-CH_2), 78.27 (C-1'), 86.86 (C-4'), 11.88 (C-2), 112.23 (C-5), 112.38 (C-3''), 117.11 (C-6), 120.38 (C-5''), 120.73 (C-1''), 126.83 (C-4''), 127.11 (C-6''), 128.29 (C-1), 131.53 (C-4), 143.76 (C-3), 147.71 (C-5'), 155.15 (C-2''), 169.40 (C=O), 171.93 (C=O).

Synthesis of 5-N-((3,4-dimethoxyphenylethyl)amino)-2,4-diethylether-1-methyl-3-*m*-hydroxy-*p*-methoxyphenyl-cyclohexen-4-ol-1, $C_{30}H_{39}NO_9$

Received from 0.19 g (0.18 ml, 1.056 g/ml, 1.2 mmol) isovaniline aldehyde, 0.33 g (0.32 ml, ϱ=1.0284 g/ml, 2.4 mmol) acetoacetic ester, 0.23 g (0.21 ml, ϱ=1.074 g/ml, 1.2

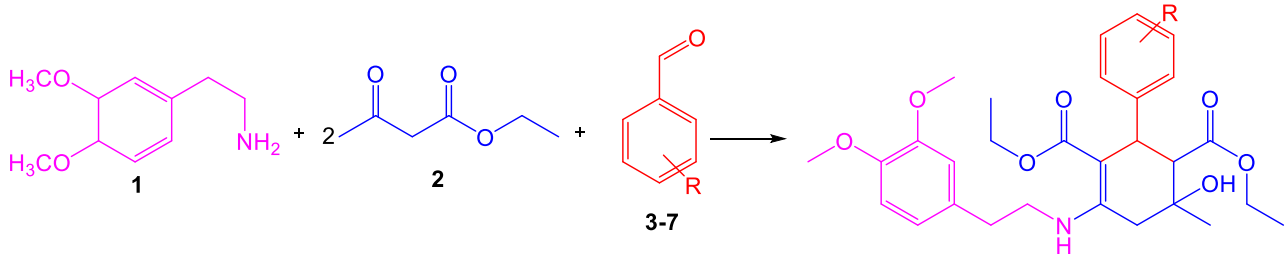
mmol) homoveratrilamine for 10 days. Yield 0.51 g (77%), oily (chloroform), *Rf* 0.76 (benzol-methanol, 6:1).

IR (KBr, ν max, cm $^{-1}$): 2953, 2836 (Ar), 1733, 1710 (C=O), 1642, 1591 (C=C), 1514 (C-C), 1441 (-CH_2-), 1365 (C-N), 1262, 1235 (C-O-C).

^{13}C NMR spectrum: (100 MHz, $CDCl_3$, δ, m.u.): 14.27 (Et-CH_3), 14.59 (Et-CH_3), 18.51 (CH_3-1'), 33.50 (C-β), 35.26 (C- 6'), 37.12 (C-2'), 41.99 (C-3'), 42.45 (C-α), 55.88 (OCH_3), 55.93 (OCH_3), 56.12 (OCH_3), 58.51 (Et-CH_2), 58.88 (Et-CH_2), 111.34 (C-1'), 120.48 (C-4'), 120.64 (C-2), 120.86 (C-5), 129.71 (C-5''), 130.35 (C-2''), 131.63 (C-6), 148.02 (C-6''), 149.22 (C-1), 158.09 (C-1''), 161.18 (C-3''), 163.39 (C-4 ''), 164.13 (C-4), 164.51 (C-3), 164.93 (C-5'), 171.67 (C=O), 191.11 (C=O).

Results and discussion

Using equimolar amounts of homoveratrilamine **(1)** reacted with acetoacetic ester **(2)** and aromatic aldehydes (**3-7**). Using method A, target products (1-Scheme) **8-12** were obtained in yields of 77–85% within 10 days. The resulting substances **10, 11** are yellowish crystals, **8, 9, 12** are oily.



R = p-N(CH_3) (3, 8)
R = *p*-OCH_3 (4, 9)
R = *p*-OH (5, 10)
R = *o*-OCH_3 (6, 11)
R = 3-OH, 4-OCH_3 (7, 12)

1-Scheme. Preparation of enaminone derivatives .

In cyclocondensation reactions occurring under these conditions, time is very important. In our previous studies [13] with other aldehydes under the same conditions, we were able to obtain a mixture of products due to the short reaction time. Accordingly, in our current reactions we increased the time to 10 days and obtained the expected three-component product in high yield (77-85%) without any additional impurities.

The results of the experiment are shown in Table 1.

1- Table .

Physico-chemical parameters of enamino-ester derivatives **8-12**

Aldehyde, R	Product, Rf	Time, day	Gross formula	Exit, %	T.m, °C
p-N(CH3)	8, 0.73	10	C31H42N2O7	82.5	oily
p-OCH3	9, 0.6	10	C30H39NO8	85	oily
p-OH	10, 0.81	10	C29H37NO8	79	168-171
o-OCH3	11, 0.8	10	C27H32NO5	80.5	155-157
3-OH, 4-OCH3	12, 0.76	10	C30H39NO9	77	oily

The structure of the obtained substances was confirmed by spectroscopy data **^{1}H NMR, ^{13}C NMR.** According to the ^{1}H NMR spectrum, the signals of the α and β protons of the methylene (CH_2-) groups of products **8-12** are shown in the field in the form of triplet and quartet 2.78-2.79 ppm . and 3.43-3.44 ppm , the proton signals in the carbon atom of the ethoxy group resonated in singlet form at 1.01-1.36 ppm. and 1.17-1.23 ppm . The signals attributed to the 2'- and 3'-carbon protons belonging to the cyclohexene ring are 2.93-3.85 ppm. and 3.86-3.96 ppm . Signals related to the 6'-carbon proton are resonant in the fields of 3.75-3.98 ppm. doublet shape, corresponding in axial and equatorial shape in the field. The signals of protons belonging to the -OH and -NH groups are shown in the fields as singlet and broadened signals at 3.75-6.15 ppm. and 8.96-9.01 ppm. Proton signals corresponding to the aromatic aldehyde residue, respectively: **8** 6.79 (2 H , d, J = 8.1, Ar -5'',6''), **9** 6.69 (1H , d, J=8.8, ArH-5), 6.73 (2H, dd , J=2.2, 8.9, ArH-2, 6) , **10** 6.71-6.74 (4H, m, ArH-2'', 3'', 5'', 6'') observed in relevant areas.

Conclusion. Cyclocondensation reactions studied homoveratrilamine and acetoacetic ester with a number of aromatic aldehydes. As a result of the reaction, a mixture of substances derived from 5-N-((3,4-dimethoxyphenylethyl)amino)-2,4-diethylether-1-methyl-3-phenyl-cyclohexen-4-ol-1 is formed. The synthesis of various enaminones in high yields has been achieved according to the [1+2+1] scheme of the reagents used using mild synthesis methods carried out in a single reactor. The structure of the synthesized substances was established using modern instrumental methods of analysis.

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