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THE SYNTHESIS OF NEW 3,5-DIALKYL (PHENYL) DERIVATIVES OF PYRROLE-2-CARBOXYLATES

Abstract: *Enamines are synthesized by the condensation of 1,3-dicarbonyl compounds with glycine ethyl ether hidrochloride. New 3,5-dialkyl and diaryl derivatives of pyrroles are synthesized from the cyclic reaction of obtaining enamines under the super base medium.*

Key words: *Pyrrole, Knorr method, pyrrole-2-carboxylate.*

Language: *English*

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Introduction

Pyrrole itself is not naturally occurring in nature. However, its derivatives are a major fragment of many natural macrocycles. Pyrrole is a component of a number of drugs, catalysts and biologically active compounds. These include vitamin B_{12}, bile pigments bilirubin and biliverdin, blood pigment heme, photosynthetic pigment chlorophyll, chlorine, bacteriochlorins and porphyrine rings of porphyrogens [1-2]. Pyrrole-containing molecules often exhibit antibacterial, antifungal, anti-inflammatory, or antitumor effects. These bioactivity properties made them significant fragments for drug industry. Atorvastatin is an antihyperlipidemic drug, alorectam is an anti-Alzaimer drug, elopiprazole is an antipsychotic drug, lorpiprazole is a tranquilizer, and tolmetin is an anti-inflammatory drug containing pyrrole ring compounds [3].

Pyrrol-2-carboxylates and carboxyamides are used as intermediates in the synthesis of lamellarins [4,5], which are natural compounds, or bromopyrrol alkaloids, such as hanisin and longamide B [6].They are also key fragments for polycyclic heterocycles such as indolons and pyrrolindolones [7].

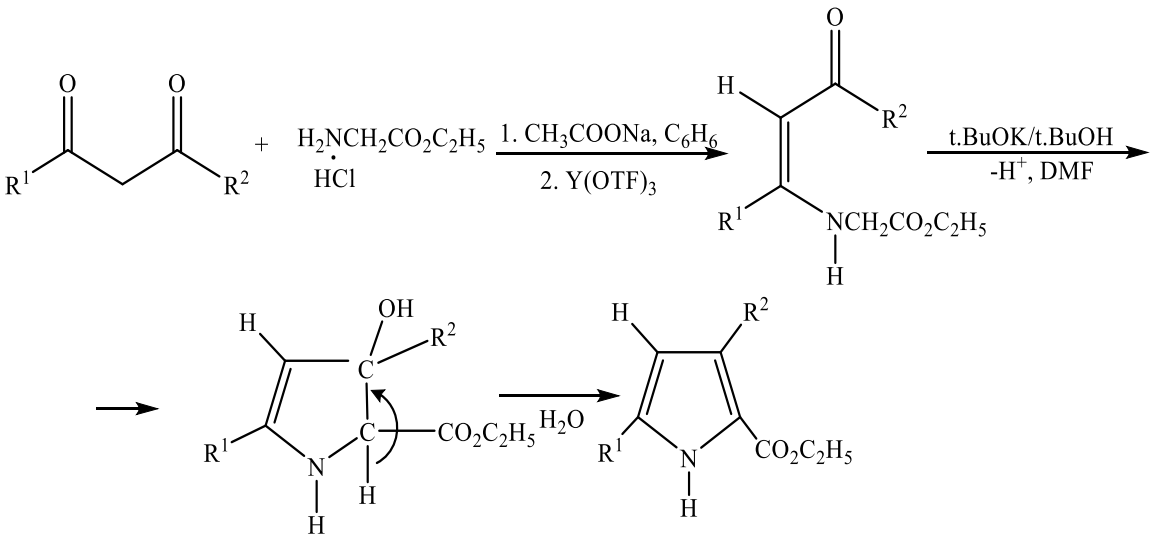
A number of methods have been developed for the synthesis of pyrrole-2-carboxylates, including the Knorr and Fischer methods [8-11]. For example metal catalyst cyclization of izosianides and alkynes [12,13], and the cycloizomerization of some functional intermediates like dienyl azids [14], homopropargyl azids [15], alkynyl aziridines [16], homoproporgyl amines [17]. The reaction of ethyl

isocyanates with nitroolefins through the Barton-Zard reaction is also used for the synthesis of compounds [18].

The synthesis of pyrroles by Paal-Knorr method from the interaction of amines with 1,4-diketones has been extensively studied [19,20]. However, studies on the synthesis of pyrrole from 1,3-dicarbonyl compounds are not large-scale. Taking this into account, the presented research work was carried out in the mentioned direction.

Result and discussion

For the synthesize of 3,5-dialkyl (phenyl)-pyrrole-2-ethyl-carboxilate derivatives at first we have synthesized enamines by the condensation 1,3-dicarbonyl compounds with glycine ethyl ester hidrochloride. As a continuation of the process, pyrrole derivatives (I-III) were synthesized from the reaction of enamines with glycine ethyl ester in the presence of *tert*-BuOK / *tert*-BuOH/ DMFA . During the reaction, *tert*-BuOK is used as a super basic medium, like in the synthesis of 2-phenylpyroles. At first we used C_2H_5ONa/ C_2H_5OH for cyclization of enamines into pyrrole derivatives with a yield of 10-42%. However, when enamines were mixed in a dimethylformamide medium at 60-70° C in the presence of *tert*-BuOK / *tert*-BuOH, derivatives of 3,5-dialkyl (phenyl) -pyrrol-2-ethyl carboxylate were synthesized with a practical yield of 45-50%. Reaction proceeded for 4-5 hours by the following scheme.



$R^1=R^2=CH_3$ (1) ; $R^1=CH_3$, $R^2=C_6H_5$ (II); $R^1=R^2=C_6H_5$ (III).

Although this type of pyrrole has been synthesized by many scientists in the literature, for the first time we have obtained 3,5-dialkyl (phenyl) -pyrrole-2-ethylcarboxylates from the reaction of enamines and glycic acid with ethyl ether in the presence of *tert*-BuOK / *tert*-BuOH.

Experimental

^1H NMR and ^{13}C NMR spectra ware recorded on a 400 spectrophotometer using in DMSO-d6 as the solvent. Chemical shifts values are reported in ppm taking tetramethylsilane as the internal standard and J values are given in hertz. The types of signals are indicated by the following letters: s=singlet, d=doublet, t=triplet, m=multiplet. Flash column chromatography (FCC) was performed by using glass columns with flash grade silica gel (70-230 mesh). Reactions were monitored by thin-layer chromatography (TCL) using pre coated silica gel plates, visualized by UV light. All organic extracts were dehydrated over oven-dried $MgSO_4$.

The synthesis of 2,4-dimethyl-2*H*-pyrrole-5-carboxilate (I)

4.18 g glycine ethyl ester hydrochloride was added to 300 mg acetyl acetone and reflux in 50 ml benzene in the presence of 5% mole $Yb(OTF)_3$ catalyst for 6 hours. At the end the reaction mixture was cooled to room temperature, washed with 100 ml water. It was then extracted three times with 50 ml CH_2Cl_2. All organic extracts were dehydrated over oven-dried $MgSO_4$ and crystallized in hexane. In the second stage of reaction, 7 ml of *tert*-BuOH and 14 ml DMFA was added to the obtained crystals and mixed. Then 1.5 g *tert*-BuOK was added to this mixture and mixed for 4-5 hours at 80°C. The mixture was cooled to room temperature, washed with 50 ml of water and extracted with 50 ml of ether. All organic extracts were dehydrated over oven-dried $MgSO_4$ and cleaned by column chromatography. Eluent n-hexane : ethyl acetate 10:1. Yellow crystals were obtained.

^{13}CNMR spectra (DMSO-*d6*), δ [ppm], m.h.: 13.14 (CH_3), 13.21(CH_3), 14.84 (CH_3), 59.27(CH_2O), 111.17 (C_{pyr}), 117.24 (=C_{pyr}), 128.24 (C_{pyr}), 133.36 (C_{pyr}), 161.38 (COO).

^{1}HNMR(300 MHz,DMSO-*d6*), δ [ppm],m.h.: 1.24 (t,3H, CH_3,); 2.12 (s, 3H, CH_3,), 2.17 (s, 3H, CH_3,), 4.18 (q, 2H, CH_2O), 5.69(s,1H,CH=), 11.08 (s,1H,NH).

The synthesis of ethyl-2-methyl-4-phenyl-2*H*-pyrrole-5-carboxylate (II)

500 mg benzoyl acetone was added to 4.30 g glycine ethyl ester hydrochloride and reflux in 100 ml benzene in the presence of 5% mole $Yb(OTF)_3$ catalyst for 6 hours. At the end the reaction mixture was cooled to room temperature, washed with 100 ml water. Then extracted three times with 50 ml CH_2Cl_2. All organic extracts were dehydrated over oven-dried $MgSO_4$ and crystalized in hexane. In the second stage of reaction 5 ml *tert*-BuOH and 10 ml DMFA was added to the obtained crystals and mixed. Then 0.67 g *tert*-BuOK was added to this mixture and stirred for 4-5 hours at 80°C. After the reaction mixture cooled to room temperature, washed with 50 ml water. Then extracted with 30 ml diethyl ether. All organic extracts were dehydrated over oven-dried $MgSO_4$ and cleaned by column chromatography. Eluent n-hexane : ethyl acetate 10:1. Yellow crystals were obtained.

^{13}CNMR spectra (DMSO-*d6*), δ [ppm], m.h.: 14.37(CH_3), 16.34 (CH_3), 60.31 (CH_2O), 111.46 (C_{pyr}), 119.29 (C_{pyr}), 127.71 (C_{pyr}), 128.96 (2 C_{ar}), 129.92 (2 C_{ar}), 132.79(C_{ar}), 135.02 (C_{ar}), 136.24 (C_{pyr}), 161.12(COO).

^{1}HNMR(300 MHz,DMSO-*d6*), δ [ppm],m.h.: 1.21 (t,3H, CH_3,); 2.16 (s,3H, CH_3,);4.16 (q, 2H, CH_2O), 6.27(s,1H,CH=); 7.36-7.79 (m,5H,Ar-H), 11.98 (s,1H,NH).

The synthesis of ethyl 3,5-diphenyl-2*H*-pyrrole -2-carboxylate (III)

500 mg dibenzoylmethane was added to 3.11 g glycine ethyl ester hydrochloride and reflux in 100 ml benzene in the presence of 5% mole $Yb(OTF)_3$ catalyst for 6 hours. At the end the reaction mixture was cooled to room temperature, washed with 200 ml water.Then extracted three times with 50 ml CH_2Cl_2. Organic phase was dried on $MgSO_4$ and crystalized in hexane. In the second stage of reaction 6 ml *tert*-BuOH and 12 ml DMFA was added to the obtained crystals and mixed. Then 1.27 g *tert*-BuOK was added to this mixture and mixed for 4-5 hours at 80°C. After the reaction mixture cooled to room temperature, washed with 50 ml water.Then extracted with 50 ml diethyl ether. All organic extracts were dehydrated over oven-dried $MgSO_4$ and cleaned by column chromatography. Eluent n-hexane : ethyl acetate 10:1. Yellow crystals were obtained.

^{13}CNMR spectra (DMSO-*d6*), δ [ppm], m.h.: 14.52(CH_3), 60.11 (CH_2O), 110.23 (C_{pyr}), 118.99 (C_{pyr}), 125.82 (2 C_{ar}), 127.18 (CH_{pyr}), 128.01 (2 C_{ar}), 129.15(2 C_{ar}), 129.78 (2 C_{ar}), 131.45 (2 C_{ar}), 132.95 (C_{ar}), 135.70 (C_{ar}), 136.16 (=C_{pyr}), 161.04 (COO)

^{1}HNMR (300 MHz,DMSO-*d6*), δ [ppm],m.h.: 1.18 (t,3H, CH_3,); 4.17 (q, 2H, CH_2O), 6.74 (s,1H,CH=); 7.30-7.90 (m,10H,2Ar), 11.94 (s,1H,NH).

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