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 hydrochloride. New 3,5-dialkyl and diaryl derivatives of pyroles 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 B₁₂, bile pigments bilirubin and biliverdin, blood pigment heme, photosynthetic pigment chlorophyll, chlorine, bacteriochlorins and porphyrine rings of porphyrogenes [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, alorcetam is an anti-Alzheimer drug, elopiprazole is an antipsychotic drug, lorpiprazole is a tranquilizer, and tolmelin 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 iosionesides and alkynes [12,13], and the cycloizomerization of some functional intermediates like dienyl azids [14], homopropargyl azids [15], alkynyl aziridines [16], homopropargyl 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 synthesis 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 hydrochloride. 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 C₂H₅ONa / C₆H₅OH 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.

![Diagram of the reaction scheme](https://example.com/diagram.png)

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 derivatives (I) as yellow crystals were obtained. For the synthesis of 3,5-dialkyl (phenyl) pyrrole derivatives (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% 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 CH₂Cl₂. All organic extracts were dehydrated over oven-dried MgSO₄ 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 MgSO₄ and cleaned by column chromatography. Eluent n-hexane : ethyl acetate 10:1. Yellow crystals were obtained.

**Experimental**

1H NMR and 13C NMR spectra were 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 (TLC) using pre coated silica gel plates, visualized by UV light. All organic extracts were dehydrated over oven-dried MgSO₄.

**The synthesis of 2,4-dimethyl-2H-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% 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 CH₂Cl₂. All organic extracts were dehydrated over oven-dried MgSO₄ 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 MgSO₄ and cleaned by column chromatography. Eluent n-hexane : ethyl acetate 10:1. Yellow crystals were obtained.

**Impact Factor:**

| Impact Factor | ISRA (India) | SIS (USA) | ICV (Poland) |
|---------------|-------------|-----------|--------------|
| GIF (Australia) | 0.564 | 0.912 | 6.630 |
| JIF | 1.500 | | 4.260 |
| JIF | | | 3.500 |

**References:**

[18] [Reference](https://example.com/)

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Philadelphia, USA
The synthesis of ethyl-2-methyl-4-phenyl-2H-pyrrole-5-carboxylic acid (II)

500 mg benzoyl acetone was added to 4.30 g glycolic acid 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 CH2Cl2. All organic extracts were dehydrated over oven-dried MgSO4 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 MgSO4 and cleaned by column chromatography. Eluent n-hexane : ethyl acetate 10:1. Yellow crystals were obtained.

13CNMR spectra (DMSO-d6), δ [ppm], m.h.: 14.37(CH3), 16.34 (CH3), 60.31 (CH2O), 111.46 (Cpyr), 119.29 (Cpyr), 127.71 (Cpyr), 128.96 (2 CAr), 129.92 (2 CAr), 132.79(CAr), 135.02 (CAr), 136.24 (Cpyr), 161.12(COOCO).

1HNMR(300 MHz,DMSO-d6), δ [ppm], m.h.: 1.21 (t,3H, CH3 ); 2.16 (s,3H, CH3 );4.16 (q, 2H, CH2O), 6.27(s,1H,CH3=); 7.36-7.79 (m,5H,Ar-H), 11.98 (s,1H,NH).

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

500 mg dibenzoylmethane was added to 3.11 g glycolic acid 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 CH2Cl2. Organic phase was dried on MgSO4 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 MgSO4 and cleaned by column chromatography. Eluent n-hexane : ethyl acetate 10:1. Yellow crystals were obtained.

13CNMR spectra (DMSO-d6), δ [ppm], m.h.: 14.52(CH3), 60.11 (CH2O), 110.23 (Cpyr), 118.99 (Cpyr), 125.82 (2 CAr), 127.18 (CH3pyr), 128.01 (2 CAr), 129.15 (2 CAr), 129.78 (2 CAr), 131.45 (2 CAr), 132.95 (CAr), 135.70 (CAr), 136.16 (=Cpyr), 161.04 (COO).

1HNMR(300 MHz,DMSO-d6), δ [ppm], m.h.: 1.18 (t,3H, CH3 ); 4.17 (q, 2H, CH2O), 6.74 (s,1H,CH3=); 7.30-7.90 (m,10H,2Ar), 11.94 (s,1H,NH).

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Impact Factor:

| Journal          | Impact Factor |
|------------------|---------------|
| ISRA (India)     | 4.971         |
| ISI (Dubai, UAE) | 0.829         |
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| JIF              | 1.500         |
| SIS (USA)        | 0.912         |
| PIIHI (Russia)   | 0.126         |
| ESJI (KZ)        | 8.997         |
| JIF              | 1.500         |
| SJIF (Morocco)   | 5.667         |
| OAJI (USA)       | 0.350         |
| ICV (Poland)     | 6.630         |
| PIF (India)      | 1.940         |
| IBI (India)      | 4.260         |

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