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RECENT ADVANCES IN THE SYNTHESIS AND STRUCTURAL ELUCIDATION OF TETRASUBSTITUTED PYRROLES UNDER SUPERBASIC CONDITION

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Pyrrole derivatives are widely recognized for their presence in biologically active natural products, pharmaceuticals, and advanced functional materials. Given their significant role in systems such as heme, chlorophyll, and vitamin B_{12}, the development of efficient synthetic approaches to functionalized pyrroles remains a crucial objective in organic chemistry. In this study, we investigated a three-step synthesis of β-substituted pyrrole derivatives based on aromatic-substituted 1,3-dicarbonyl compounds and 2,3-dibromoprop-1-ene. New 2-phenyl tetra substituted pyrroles were synthesized in a superbasic medium comprising t-BuOK/DMSO in *t*-BuOH. The structure of new synthesized compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy.

Keywords: pyrole ring, β-ketoesters, dicarbonyl compounds, enamines, porphyrin ring

INTRODUCTION

Pyrrole itself does not exist freely in nature. Pyrroles represent a significant class of five-membered heterocyclic compounds containing one nitrogen atom, widely recognized for their presence in biologically active molecules, natural products, and pharmaceuticals. Examples include vitamin B_{12}, the bile pigments bilirubin and biliverdin, the blood pigment heme, chlorophyll, chlorins, bacteriochlorins, and porphyrinogens, all of which contain porphyrin rings [1]. For instance, heme and chlorophyll possess a porphyrin ring composed of four pyrrole units. Pyrrole structures are integral to various biologically active compounds, including antibiotics, toxins, cell division inhibitors, and immunomodulators. Notable examples include pyrrolomycins, which are polyhalogenated antibiotics with a stable nitropyrrole nucleus, exhibiting potent antibacterial and immunomodulatory activities [2, 3].

Among pyrrole dervatives, tetrasubstituted pyrroles, characterized by four different or similar substituents attached to the pyrrole ring, have attracted considerable attention due to their structural diversity and broad spectrum of biological activities. These derivatives often exhibit anti-inflammatory, anticancer, antimicrobial, and antiviral properties, making them valuable scaffolds in medicinal chemistry [4, 5]

The synthesis of tetrasubstituted pyrroles poses a compelling challenge in heterocyclic chemistry. Traditional synthetic strategies, such as the Paal-Knorr, Hantzsch, and Knorr methods, have been widely used but often lack the regioselectivity or functional group compatibility needed for complex substitution patterns. As a result, the development of efficient, selective, and versatile methods for the construction of tetrasubstituted pyrrole rings remains a major focus in modern organic synthesis [6].

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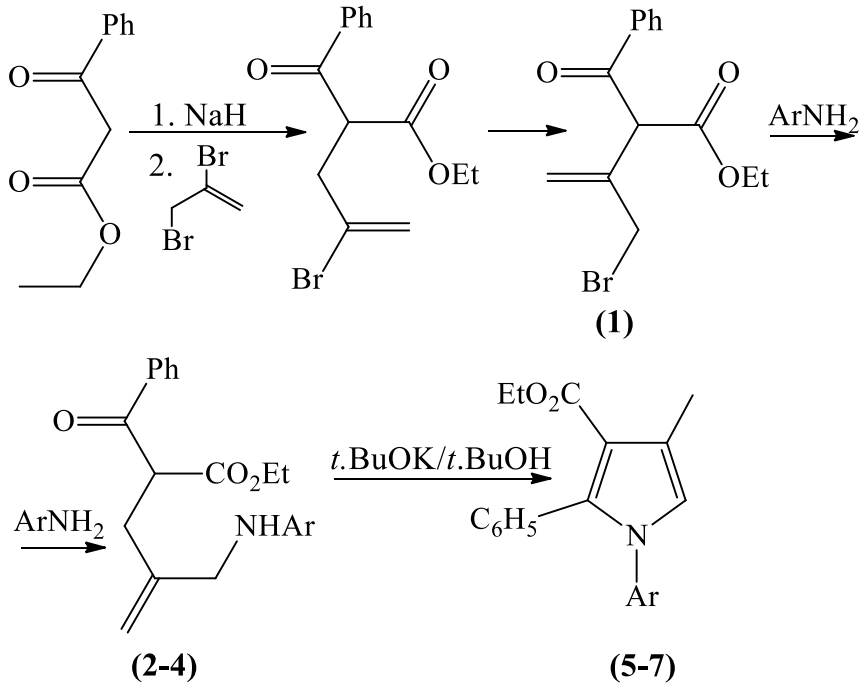
In the literature, various approaches to the synthesis of tetrasubstituted pyrroles are available The main challenge for researchers working in this field is to develop practically convenient cyclization methods based on easily accessible starting compounds [7, 8].

This growing interest underscores the importance of exploring new synthetic methodologies for tetrasubstituted pyrroles, particularly those that utilize readily available starting materials and environmentally benign conditions.

RESULTS AND DISCUSSION

In this study, we investigated a three-step synthesis of 2-phenyl-tetrasubstituted pyrrole derivatives based on aromatic-substituted 1,3-dicarbonyl compounds and 2,3-dibromoprop-1-ene.

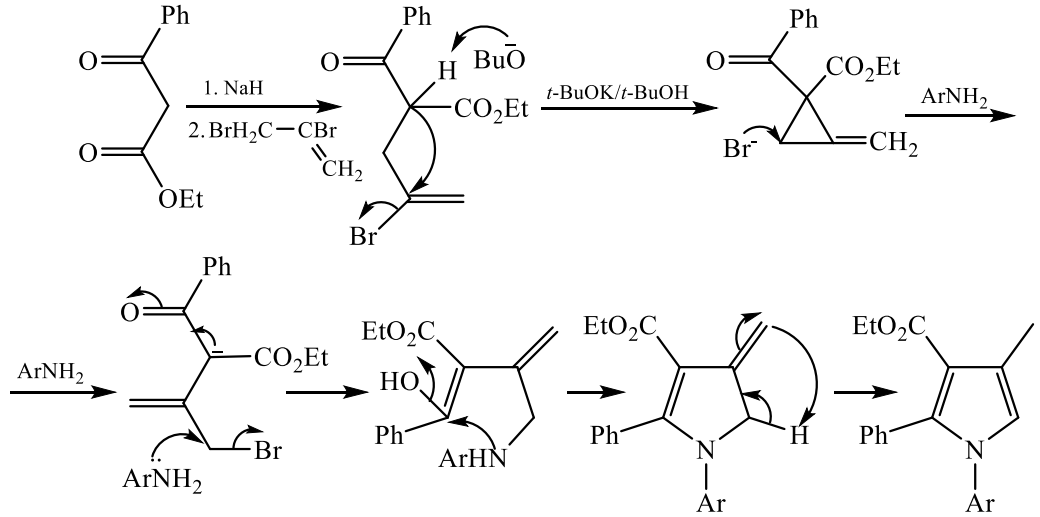
Building upon this foundation and as a continuation of the above mentioned studies, the current work aims to investigate suitable reaction systems based on aromatic-substituted 1,3-dicarbonyl compounds and 2,3-dibromoprop-1-ene. The primary objective is to study how the nature of the aromatic fragment influences the course, direction, and yield of the reaction. In our studies, similar transformations were carried out on 2-bromoallyl derivatives of aliphatic 1,3-dicarbonyl compounds in a superbasic medium, resulting in the synthesis of the corresponding pyrroles [9, 10].



Ar= C_6H_5 (5), C_6H_5 -CH_2 (6), C_6H_5 (CH_3)CH (7)

As seen from the reaction scheme above, the synthesis process proceeds in three stages. Initially, the regiospecific alkylation of β-ketoester with 2,3-dibromopropene yields ethyl 2-benzoyl-3-(bromomethyl)but-3-enoate (1). This synthesis has been previously reported in the literature, achieving yields of 85–92%. In a benzene medium and in the presence of *p*-TsOH, the reaction of ethyl 2-benzoyl-3-(bromomethyl)but-3-enoate with aromatic amines leads to the formation of enamines (2–4) in 83–95% yield.

The conversion of these enamines into pyrroles is carried out in a superbasic medium, specifically a mixture of t-BuOK/DMSO in *t*-BuOH. To enhance the yield, this superbasic system *t*-BuOK/DMSO in *t*-BuOH was further optimized . As known, the tert-butoxy group is a very strong base, and therefore finds wide application in organic synthesis.



According to the proposed reaction mechanism, the process begins with the elimination of a proton from the methylene group of the 1,3-dicarbonyl compound in the presence of sodium hydride and the resulting enolate performs an SN2 attack on 1,2-dibromoethene forming bromo-alkene intermediate. The base abstracts a proton adjacent to the bromoalkene group. This forms a carbanion, which attacks the β-carbon of the alkene intramolecularly and in the result a cyclopropane ring forms with elimination of Br^- anion. This is followed by the attack of the Br^- anion on the newly formed ring, facilitating rearrangement. The attack of the aryl amine on the intermediate results in the formation of an enamine, which undergoes several transformations to afford the corresponding β-substituted pyrrole derivatives.

EXPERIMENTAL

Synthesis of 2-Benzoyl-4-bromoethylpent-4-enoate (1)

To a solution of 960 mg (5 mmol) of benzoyl acetate dissolved in 5 mL of dry tetrahydrofuran (THF), 120 mg (5.0 mmol) of NaH was added under a dry nitrogen atmosphere. The mixture was stirred at room temperature for 2 hours. Then, a solution of 1 g (5.0 mmol) of 2,3-dibromopropene in 5 mL of THF was added, and stirring was continued for an additional 3 hours.

The reaction mixture was subsequently treated with water and then with a 2–3% aqueous HCl solution. The resulting mixture was extracted with ether (3 × 25 mL), and the organic phase was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (eluent: ethyl acetate = 1:4). The obtained product was a viscous yellow liquid, Rf = 0.54, b.p. 126–127 °C

Synthesis of Enamines Based on 2-Benzoyl-4-bromoethylpent-4-enoate (2–4)

Enamines (2–4) were synthesized according to the following method: 0.01 mol of 2-benzoyl-4-bromoethylpent-4-enoate, 0.015 mol of the corresponding amine, and a catalytic amount of p-toluenesulfonic acid (PTSA) were dissolved in 20 mL of benzene and refluxed for 10 hours in a Dean–Stark apparatus. After standing at room temperature overnight, the mixture was purified by column chromatography.

2-Bromo-5-phenylaminoethylpent-4-enoate (2)

^{1}H NMR (400 MHz, $CDCl_3$, δ) : 1.25 (t, J= 7.0 Hz, 3H, CH_3); 3.45 (s, 2H, CH_2); 4.20 (k, J= 7.0 Hz, 2H, CH_2); 5.40 (s, 1H, CH); 5.55 (s, 1H, CH_2); 7.00-7.61 (m, 10H, CH_{ar}); 10.0 (s, 1H, NH).

Ethyl 4-methyl-1,2-diphenyl-1H-pyrrole-3-carboxylate (5)

The compound was obtained as a viscous liquid, 1.89 q (75%). IR spectrum (film, cm^{-1}): 3040, 2920, 1650, 1560, 1280, 1198 sm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.25 (t, J= 7.0 Hz,

3H, CH_3); 2.30 (s, 3H, CH_3); 4.20 (k, J= 7.0 Hz, 2H, CH_2); 6.80 (s, 1H, CH_{pir}); 7.00-7.61 (m, 10H, CH_{ar}).

^{13}C NMR (100 MHz, $CdCl_3$, δ): 13.9 (CH_3); 14.2 (OCH_2CH_3); 58.09 (OCH_2CH_3); 77.08 (C_{pyrr}); 99.10 (C_{pyrr}); 115.0 (C_{pyrr}); 118.2 (CH_{pyrrr});123.0 (C_{pyrr}), 128.0-133.0 (CH_{ar}); 134.2 (C_{ar}); 139.0 (C_{ar}); 164.5 (C=O).

Ethyl 1-benzyl-4-methyl-2-phenyl-1H-pyrrole-3-carboxylate (6)

The compound was obtained as a viscous liquid, 2.2 g (82% yield). IR spectrum (film, cm^{-1}): 3040–2970, 1540, 1425, 1380.

^1H-NMR (400 MHz, $CDCl_3$, δ) : 1.14 (t., 7.0 Hz, 3H, CH_3); 2.10 (s, 3H, CH_3); 4.12 (k, J=7.0 Hz, 2H, CH_2); 6.55 (s, 1H, CH); 7.00-7.50 (m, CH_{ar}, 10H).

^{13}C NMR spektri (100 MHz, $CdCl_3$, δ) : 12.5 (CH_3); 14.6 (CH_3); 48.4 (CH_2); 60.0 (CH_{pyrr}); 98.2 (C_{pyrr}); 110.2 (CH_{ar}); 125.6 (CH_{ar}); 127.4 (CH_{ar}); 127.8 (CH_{ar}); 127.9 (CH_{ar}); 129 (CH_{ar}); 130.6 (C_{pyrr}); 132.6 (C_{pyrr}); 137.8 (C_{ar}), 138.4 (N–C_{ar}); 164.8 (CO).

(R)-Ethyl 4-methyl-2-phenyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate (7)

The compound was obtained as a yellow viscous liquid in 1.9 g yield (70%). Optical rotation: $[\alpha]_D^{20}$ = +184° (c = 0.47, $CHCl_3$). IR spectrum (film, cm^{-1}): 3050, 2980, 1675, 1535.

^1H-NMR (400 MHz, $CdCl_3$, δ) : 1.1 (t, CH_3, 3H, J= 7.0 Hz); 1.78 (d, 3H, CH_3, J= 7.1 Hz); 6.38 (s,1H, CH); 7.0 (d, J=7.5 Hz, 2H, CH_2), 7.2-7.50 (m, 8H, CH_{ar}).

^{13}C-NMR (100 MHz, $CdCl_3$, δ) : 14.2 (OCH_2CH_3); 14.3 (CH_3); 19.1(CH_3), 53.2 (N-CH); 59.0 (OCH_2CH_3); 110.8 (CH_{pyrr}); 113.0 (C_{pirr}); 126.0 (C_{pyrr}); 127.2 (C_{pyrr}); 128.0-133.0 (CH_{ar}); 139.2 (C_{ar}); 142.4 (C_{ar}); 164.5 (C=O).

CONCLUSION

In this study, a series of novel tetrasubstituted pyrrole derivatives were successfully synthesized under superbasic conditions. The key intermediate, 2-benzoyl-4-bromoethylpent-4-enoate, was obtained via alkylation of benzoylacetate and further transformed into a variety of enamine and pyrrole compounds. Among the synthesized compounds, optically active and structurally diverse pyrroles, including (R)-ethyl 4-methyl-2-phenyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate, were prepared in good to excellent yields.

The structures of the synthesized compounds were confirmed by spectroscopic methods, including ^1H and ^{13}C NMR, IR, and TLC analysis. NMR data recorded on a Bruker DPX 400 spectrometer ($CDCl_3$) and IR spectra obtained from a Perkin Elmer 1600 FTIR spectrometer confirmed the successful formation of the target molecules. TLC monitoring under UV light (λ = 254 nm) verified the purity of the compounds.

The efficient synthetic procedures, along with the structural elucidation of the newly obtained pyrrole derivatives, provide a valuable contribution to the field of heterocyclic chemistry and may serve as a foundation for further studies on their potential biological applications.

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