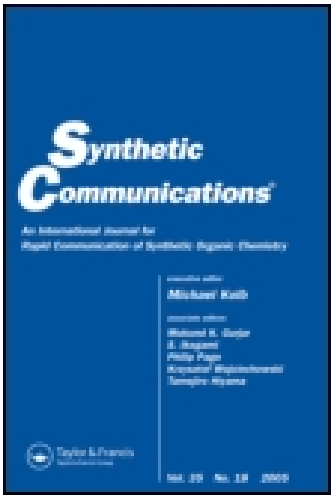


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# Synthesis and Characterization of Some Novel Multisubstituted 6,7-Dihydro-5H-cyclopenta[b]pyridine Derivatives

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# SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL MULTISUBSTITUTED 6,7-DIHYDRO-5*H*-CYCLOPENTA[*b*]PYRIDINE DERIVATIVES

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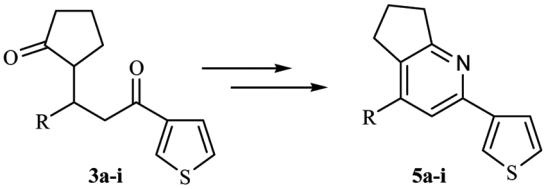
*Department of Chemistry, Faculty of Arts and Sciences, Gaziosmanpasa University, Tokat, Turkey*

## GRAPHICAL ABSTRACT




a) R = Ph, b) R = *p*-Cl-$C_6H_4$, c) R = *p*-Br-$C_6H_4$, d) R = *p*-$CH_3$-$C_6H_4$, e) R = *p*-$OCH_3$-$C_6H_4$, f) R = *m*-Br-$C_6H_4$, g) R = *m*-$CH_3$-$C_6H_4$, h) R = *o*-$OCH_3$-$C_6H_4$, i) R = thiophen-2-yl

**Abstract** *In this study, we describe systematic preparation of a series of aryl-substituted pyridine derivatives. The 1,5-dicarbonyls (**3a–i**) were prepared in the solvent-free conditions starting from chalcone derivatives (**1a–i**). The target compounds, 4-aryl-2-(thiophen-3-yl)-6,7-dihydro-5*H*-cyclopenta[b]-pyridine derivatives (**5a–i**), were synthesized by a cyclization reaction of the 1,5-dicarbonyls (**3a–i**) with ammonium acetate ($NH_4OAc$) in acetic acid. The characterization of synthesized compounds was proved by elemental analyses, infrared, mass spectrometry, and $^1H$ and $^{13}C$ NMR spectroscopy.*

*[Supplementary materials are available for this article. Go to the publisher's online edition of* Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

**Keywords** 4-Aryl-2-(thiophen-3-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]-pyridine; chalcone; 1,5-dicarbonyl

## INTRODUCTION

Thiophenes[1–3] and pyridines[4] are among the most important five- and six-membered heterocycles. Additionally, thiophene units are available in many compounds of materials science.[5–7] In particular, the pyridine substructure, as organic electronic material,[8,9] is very common in biologically active and pharmaceutically relevant compounds[10,11] as well as in building blocks used in supramolecular chemistry.[12–14]

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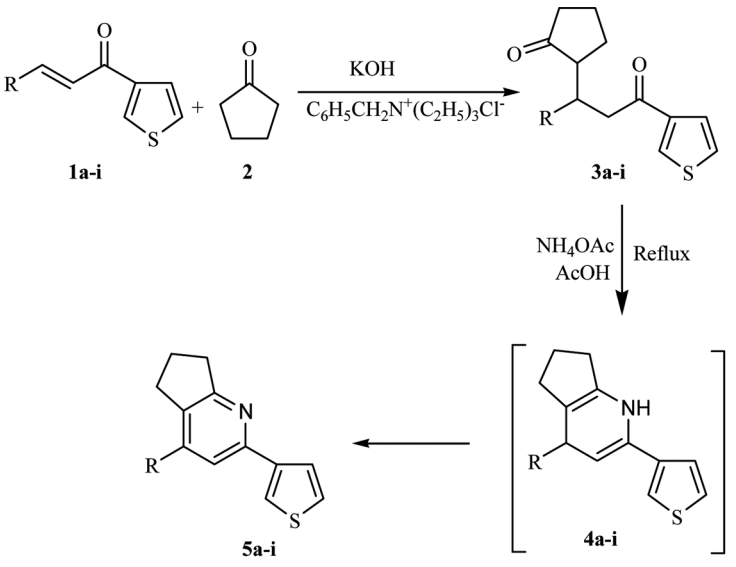
The synthesis of highly substituted pyridines is of special interest because they are partial structures of many natural products, pharmaceuticals, and organic functional materials.[15] It has been reported in the literature that substituted pyridine derivatives display antitumor activity, topoisomerase (topo) I and II inhibitory activities, cytotoxicity, and antiasthmatic, antibacterial, antiinflammatory, and antihypertensive properties.[16–20] Particularly, alkyl-substituted pyridines are widely used in many fields including applied chemistry, polymer, and pharmacological industries.[21] Also, the alkyl derivatives of pyridines are often by-products in many industrial processes: as mixtures they are relatively cheap and effective enough to protect the steel surface against acid corrosion.[22,23]

The aim of this study is to synthesize novel 4-aryl-2-(thiophen-3-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine derivatives (**5a–i**) through cyclization reactions of 1,5-diketone derivatives (**3a–i**) with ammonium acetate in the presence of acetic acid.



## RESULTS AND DISCUSSION

The chalcone drivatives (**1a–i**) were easily synthesized according to our previously published procedure.[24,25] Then, the 1,4-Michael addition of cyclopentanone (**2**) to the chalcone derivatives (**1a–i**) gave the 1,5-dicarbonyls (**3a–i**).[26,27] This addition was performed in basic medium (KOH) in the presence of benzyltriethylammonium chloride at room temperature (Scheme 1). Addition of cyclopentanone (**2**)




a) R = Ph, b) R = *p*-Cl-$C_6H_4$, c) R = *p*-Br-$C_6H_4$, d) R = *p*-$CH_3$-$C_6H_4$, e) R = *p*-$OCH_3$-$C_6H_4$, f) R = *m*-Br-$C_6H_4$, g) R = *m*-$CH_3$-$C_6H_4$, h) R = *o*-$OCH_3$-$C_6H_4$, i) R = thiophen-2-yl

**Scheme 1.** Synthesis of 1,5-dicarbonyls (**3a–i**) and 4- aryl-2-(thiophen-3-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]-pyridine derivatives (**5a–i**).

to the chalcone derivatives (**1a–i**) was performed in solvent-free conditions. 1,5-Dicarbonyl derivatives (**3a–i**) were obtained in good yields (in the range of 70–92%) (Table 1). The crude products were purified by chromatography or crystallization, and their structures were elucidated by spectroscopic methods. In the $^1$H NMR spectrum of **3a–i**, the protons of $PhCOCH_2$ gave an AB system that is characteristic for these compounds. While the part A of the AB system is shown as a doublet of doublets at $\delta = 3.42–3.20$ ($J = 17.6–15.6$ and 8.0–7.2 Hz), part B is shown as a doublet of doublets at $\delta = 3.28–3.04$ ($J = 17.6–15.4$ and 7.6–6.8 Hz).

Finally, the 4-aryl-2-(thiophen-3-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine derivatives (**5a–i**) were obtained by the cyclization reaction of 1,5-dicarbonyls (**3a–i**) in the presence of ammonium acetate in acetic acid (Scheme 1). We think that the oxidation occurred by effect of air oxygen. The structures of the synthesized cyclization products (**5a–i**) were elucidated by the spectroscopic methods. In the $^1$H NMR spectrum of **5a–i**, the H3 proton gave a singlet (between $\delta = 9.19$ and 8.08 ppm) that is characteristic signals for these compounds. All spectral data confirm the proposed structures.

As a result, we have described a mild, efficient, and convenient method for the synthesis of 4-aryl-2-(thiophen-3-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine derivatives from cheap and easily available materials such as 1-(thiophen-3-yl)ethanone, benzaldehyde derivatives, cyclopentanone, and ammonium acetate.



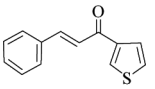
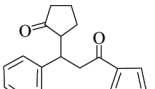
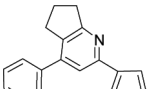
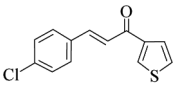
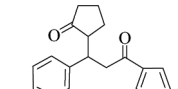
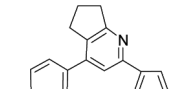
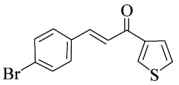
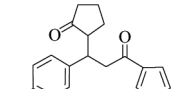
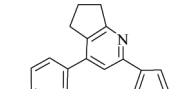
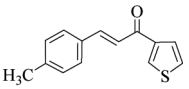
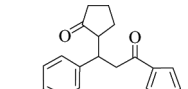
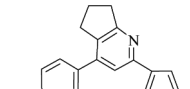
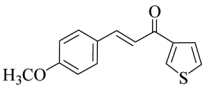
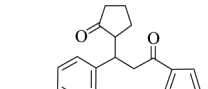
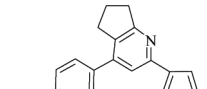
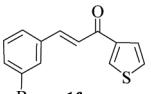
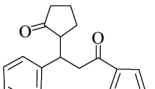
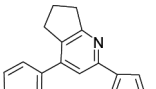
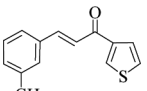
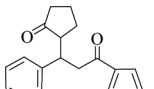
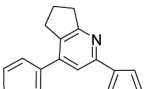
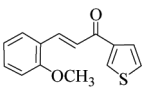
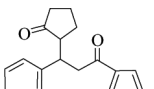
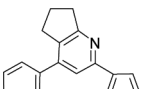
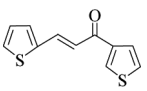
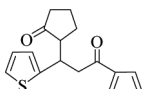
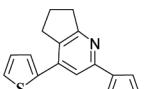
## EXPERIMENTAL

All reagents were dried and distilled by standard procedures. Melting points were measured on an Electrothermal 9100 apparatus. Infrared (IR) spectra (KCl or liquid) were recorded on a Jasco FT/IR-430 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance III 400 instrument. Internal standards tetramethylsilane (TMS) ($\delta$ 0.00) for $^1$H NMR and $CDCl_3$ ($\delta$ 77.0) for $^{13}$C NMR spectroscopy were used, and $J$ values are given in hertz (Hz). The multiplicities of the signals in the $^1$H NMR spectra are abbreviated by s (singlet), d (doublet), t (triplet), q (quarted), p (pentuplet or quintuplet), m (multiplet), br (broad), and combinations thereof. Elemental analyses were obtained from a Leco CHNS 932 Elemental Analyzer.

### General Procedure for the Synthesis of 1,5-Diketone Compounds (3a–i)[24,25]

Benzyltriethylammonium chloride (6% mol) and KOH (6% mol) were added to a mixture of chalcone derivatives (**1a–i**) (5 mmol) and cyclopetanone (**2**) (20 mmol). The reaction mixture was magnetically stirred at room temperature for 3–6 h. The crude product was dissolved with chloroform (10 mL), neutralized by 2% HCl solution and extracted by chloroform ($2 \times 10$ mL). The organic layer was dried over $Na_2SO_4$, and the solvent was removed in a vacuum. The raw product was purified by crystallization from $CHCl_3$/*n*-hexane (1:4) and/or $CCl_4$/*n*-hexane (2:3).

**Table 1.** Synthesized compounds **3a–i** and **5a–i**

| Reactant | Product **3a–i** | Melting point (°C) and yield (%) | Product **5a–i** | Melting point (°C) and yield (%) |
|---|---|---|---|---|
|  **1a** |  **3a** | 108–111, 85 |  **5a** | 102–105, 92 |
|  **1b** |  **3b** | 113–116, 86 |  **5b** | 130–133, 95 |
|  **1c** |  **3c** | 115–117, 80 |  **5c** | Viscous oil, 89 |
|  **1d** |  **3d** | 136–139, 92 |  **5d** | Viscous oil, 81 |
|  **1e** |  **3e** | 129–133, 72 |  **5e** | Viscous oil, 88 |
|  **1f** |  **3f** | 120–122, 80 |  **5f** | Viscous oil, 86 |
|  **1g** |  **3g** | 89–92, 85 |  **5g** | Viscous oil, 88 |
|  **1h** |  **3h** | 128–130, 79 |  **5h** | 108–112, 93 |
|  **1i** |  **3i** | Viscous oil, 70 |  **5i** | Viscous oil, 84 |

### General Procedure for the Synthesis of 4-Aryl-2-(thiophen-3-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine Derivatives (5a–i)[26,27]

Ammonium acetate ($NH_4OAc$) (4.5 mmol) was added to a solution of 1,5-dicarbonyls (**3a–i**) (1.5 mmol) in 25 mL of acetic acid and refluxed in open system for 2–6 h. Then, the acetic acid was removed under reduced pressure; the crude product was extracted by chloroform ($3 \times 10$ mL) and dried over $Na_2SO_4$. After removal of the solvent, the crude product was purified on a silica-gel column eluting with $CH_2Cl_2$/*n*-hexane (1:3) and/or crystallized from $CHCl_3$/*n*-hexane (1:2).

## FUNDING

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## SUPPORTING INFORMATION

Full spectral data and melting points can be found via the "Supplementary Content" section of this article's Web page.

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