Multicomponent Approach to the Synthesis of 4-(1H-indol-3-yl)-5-(4-methoxyphenyl)furan-2(5H)-one

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Abstract: A simple one-pot approach was developed for the synthesis of furan-2(5H)-one derivative containing indole fragments. This method includes the telescoped multicomponent reaction of indole, 4-methoxyphenylglyoxal, and Meldrum’s acid. The synthetic utility of the prepared furan-2(5H)-one was demonstrated by condensation with 4-methoxybenzaldehyde. The advantages of this method include the employment of readily accessible starting materials, atom economy, process simplicity, and the easy isolation of the target products. The structure of the synthesized furanones was confirmed by 1H and 13C-NMR spectroscopy and high-resolution mass spectrometry with electrospray ionization (ESI-HRMS).

Keywords: furan-2(5H)-one; indole; arylglyoxals; Meldrum’s acid; multicomponent reaction

1. Introduction

Furan-2(5H)-one derivatives (γ-butenolides) are a very important class of heterocyclic compounds thanks to their natural occurrence and noteworthy biological activities [1–3]. As an example, the cardiotonic properties of steroids containing furanone moiety (cardenolides) are well documented [4,5]. Various compounds containing the γ-butenolide core possess cytotoxic [6], antibacterial [7], and anti-inflammatory activities [8,9]. In addition, furan-2(5H)-one derivatives have been tested as peroxisome proliferator-activated receptors (PPARα) agonists employed in the treatment of dyslipidemia and diabetes [10].

Various methods for the synthesis of the butenolide core are described in the literature. Most often, gamma-keto acids and their derivatives are used as starting compounds [11,12], the intramolecular cyclization of which leads to furan-2-ones. Another common approach is the use of transition-metal-catalyzed coupling reactions [13,14]. Although many methods are known regarding the synthesis of furan-2(5H)-one moiety [15–18], some examples of multicomponent reactions (MCRs) used for the preparation of γ-butenolides are presented in the literature [19–23].

It should be noted the indole is one of the most widespread classes of heterocyclic compounds presented in the variety of natural products and synthetic biologically active substances [24–28]. In this regard, the introduction of an indole substituent into the structure of furan-2(5H)-one can lead to the essential modification of the pharmacological properties. Thus, the elaboration of a novel multicomponent approach to the synthesis of furan-2(5H)-ones containing indole substituents is of great interest.

2. Results and Discussion

Herein, we disclosed a highly efficient approach to 4-(1H-indol-3-yl)-5-(4-methoxyphenyl) furan-2(5H)-one 1 on the basis of the MCR of indole 2, 4-methoxyphenylglyoxal 3, and Meldrum’s acid 4 (Scheme 1). Previously, we have shown that the analogous synthesis of substituted furan-2(5H)-ones containing 4H-chromen-4-one fragment is a two-stage telescoped process [26,29]. Whereas, the starting step includes the interaction of components in acetonitrile (MeCN) to form unstable intermediates, which under the action of acidic
reagents are transformed into the final products. In the present communication, it was demonstrated that for the synthesis of target compound 1, the optimal conditions are the reflux in MeCN for 1 h with the use of triethylamine as the basic reagent. Further reflux in acetic acid (AcOH) for 30 min allows to synthesizing furanone 1 with a 74% yield.

Scheme 1. Synthesis of 4-(1H-indol-3-yl)-5-(4-methoxyphenyl)furan-2(5H)-one 1.

A plausible pathway of the considered process is demonstrated in Scheme 2. At first, the condensation of Meldrum’s acid 4 with arylglyoxal 3 results in the formation of a Michael acceptor A. Then, adduct B is formed via the subsequent addition of indole 2 to intermediate A. Next, the acid-catalyzed intramolecular cyclization of the intermediate D includes the enolization of carbonyl moiety and the interaction of the hydroxy group with Meldrum’s acid fragments. The elimination of CO₂ and acetone molecules leads to furan-2(3H)-ones E. The conclusive step of the process is the isomerization of E into target furan-2(5H)-one 1.

Scheme 2. Proposed reaction mechanism for the formation of furan-2(5H)-one 1.

The synthetic utility of the synthesized 4-(1H-indol-3-yl)-5-(4-methoxyphenyl)furan-2(5H)-one 1 is shown by reaction with 4-methoxybenzaldehyde 5. As a result of the interaction, a previously unknown 4-(1H-indol-3-yl)-3-(4-methoxybenzylidene)-5-(4-methoxyphenyl) furan-2(3H)-one 6 was obtained with a 84% yield. The use of an equivalent amount of piperidine in the refluxing ethanol for 1 hour is the optimal conditions for the considered condensation (Scheme 3).

In conclusion, we elaborated a novel efficient method for the synthesis of 4-(1H-indol-3-yl)-5-(4-methoxyphenyl)furan-2(5H)-one 1. This approach based on the telescoped multicomponent condensation of indole 2, 4-methoxyphenylglyoxals 3, and Meldrum’s acid 4. The synthetic utility of the prepared furan-2(5H)-one 1 was demonstrated by reaction with 4-methoxybenzaldehyde 5.
3. Materials and Methods

All starting chemicals and solvents were commercially available and were used as received. NMR spectra were recorded with a Bruker AM 300 (300 MHz) spectrometer in DMSO-\textit{d}_6. Chemical shifts (ppm) were given relative to solvent signals (DMSO-\textit{d}_6: 2.50 ppm (\textit{1}H NMR) and 39.52 ppm (\textit{13}C NMR)). High-resolution mass spectra (HRMS) were obtained on a Bruker microTOF II instrument using electrospray ionization (ESI). The melting points were determined on a Kofler hot stage.

3.1. Synthesis of 4-(1H-Indol-3-yl)-5-(4-methoxyphenyl)furan-2(5H)-one 1

A solution of indole 2 (2 mmol, 0.23 g), 4-methoxyphenylglyoxal hydrate 3 (2.2 mmol, 0.4 g), Meldrum’s acid 4 (2.7 mmol, 0.39 g), and Et\textsubscript{3}N (2.5 mmol, 0.35 mL) in 6 ml of MeCN was refluxed for 1 h. Then, the mixture was evaporated in vacuo. Six milliliters of AcOH were added to the residue, and the obtained solution was refluxed for 0.5 h and evaporated in vacuo. The residue was recrystallized from EtOH (6 ml). The precipitate formed was collected by filtration and washed with EtOH (3 × 5 mL).

Brown powder; yield: 74% (0.45 g); mp 197–199 °C. \textit{1}H NMR (300 MHz, DMSO-\textit{d}_6) δ 11.78 (br.s, 1H), 7.99–7.91 (m, 1H), 7.48–7.43 (m, 2H), 7.35 (d, \textit{J} = 8.7 Hz, 2H), 7.26–7.15 (m, 2H), 6.93 (d, \textit{J} = 8.7 Hz, 2H), 6.65–6.56 (m, 2H), and 3.72 (s, 3H). \textit{13}C NMR (75 MHz, DMSO-\textit{d}_6) δ 173.8, 161.4, 159.8, 136.6, 129.8, 129.4, 125.0, 122.8, 121.4, 120.2, 114.3, 112.4, 107.0, 106.8, 82.9, and 55.1. HRMS (ESI-TOF) \textit{m/z}: [M + H]\textsuperscript{+} Calcd for C\textsubscript{19}H\textsubscript{15}NO\textsubscript{3} 306.1125; found: 306.1131.

3.2. Synthesis of 4-(1H-Indol-3-yl)-3-(4-methoxybenzylidene)-5-(4-methoxyphenyl)furan-2(3H)-one 6

The mixture of furan-2(5H)-one 1 (1 mmol, 0.31 g), 4-methoxyaldehyde 5 (1.2 mmol, 0.16 g), and piperidine (1 mmol, 0.099 mL) was refluxed for 1 h in 6 ml of EtOH. The reaction mixture was cooled, filtered off and washed with EtOH (3 × 5 mL).

Red powder; yield: 84% (0.36 g); mp 253–255 °C. \textit{1}H NMR (300 MHz, DMSO-\textit{d}_6) δ 11.55 (br.s, 1H), 8.09 (d, \textit{J} = 9.0 Hz, 2H), 7.58–7.47 (m, 2H), 7.35 (d, \textit{J} = 9.0 Hz, 2H), 7.20–7.12 (m, 2H), 7.01–6.90 (m, 3H), 6.86–6.77 (m, 3H), 3.80 (s, 3H), and 3.70 (s, 3H). \textit{13}C NMR (75 MHz, DMSO-\textit{d}_6) δ 165.9, 161.3, 159.8, 146.8, 138.9, 136.5, 133.8, 127.6, 126.7, 126.0, 125.5, 121.7, 121.2, 119.5, 119.1, 114.1, 114.0, 112.1, 111.4, 111.3, 103.8, 55.4, and 55.2. HRMS (ESI-TOF) \textit{m/z}: [M + H]\textsuperscript{+} Calcd for C\textsubscript{27}H\textsubscript{21}NO\textsubscript{4} 424.1543; found: 424.1539.

Supplementary Materials: The following are available online. Copies of \textit{1}H, \textit{13}C-NMR, and mass spectra for compound 1 and compound 6.

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