Synthesis and Antimicrobial Evaluation of Some Chalcones and Their Derived Pyrazoles, Pyrazolines, Isoxazolines, and 5,6-Dihydropyrimidine-2-(1H)-thiones

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Received April 11, 2007; accepted April 20, 2007; published online June 29, 2007
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Summary. Chalcones were synthesized by a base catalyzed Claisen-Schmidt condensation reaction. Bromination of chalcones afforded the dibromo derivatives. Monobromo derivatives could be obtained by treating the corresponding dibromochalcones with dry benzene in the presence of triethylamine. Pyrazole derivatives were obtained by refluxing of dibromochalcones with phenylhydrazine or 2,4-dinitrophenylhydrazine in dry pyridine. Chalcones were treated with hydrazine hydrate or phenyl hydrazine in ethanol to afford 1,2-pyrazolines and N-phenyl-1,2-pyrazolines. Condensation of chalcones with hydroxylamine hydrochloride or thiourea in ethanolic sodium hydroxide solution gave 4,5-dihydroisoxazoles and 5,6-dihydropyrimidine-2-(1H)-thiones. The prepared compounds were tested for antimicrobial activity against four different bacterial species displaying different degrees of antibacterial activities or inhibitory actions.

Keywords. Chalcones; Pyrazoles; Pyrazolines; Isoxazolines; 2-Thioxopyrimidines.

Introduction

For a structurally simple group of compounds, chalcones have displayed an impressive array of biological activities, among which anti-malarial [1], anti-protozoal [2], anti-inflammatory [3], immunomodulatory [4], nitric oxide inhibition [5], tyrosinase inhibition [6], cytotoxic [7], and anticancer [8] activities have been cited in literature. These compounds obtained by convenient synthesis methods strongly inhibit the polymerization of tubulin by binding to the colchicine-binding site [9]. The relatively simple structure and high affinity of chalcones for the colchicine-binding site because of similarity of the two-aryl group placements in the two molecules has led to the synthesis and subsequent evaluation of a large number of chalcones [10]. The synthesis of arylpyrazoles is of major interest [11]. Indeed these constitute an important class of heterocyclic compounds because this ring system is present in numerous compounds of therapeutic importance including a number of marketed drugs, such as Celecoxib (Celebrex®) or Deracoxib (Fig. 1) [12]. Due to the importance of these pharmacological properties, significant efforts toward the synthesis of this kind of compounds have been carried out in the last years [13]. Functionalized isoxazolone and isoxazole derivatives are active pharmacophores in several pharmacologically important molecules [14], and are also useful intermediates for the synthesis of a wide variety of bioactive natural products [15]. Thioxopyrimidine is an essential structural unit of several heterocycles, which display a wide range of interesting biological and pharmacological properties, such as anticancer and antimicrobial activities [16]. Despite these characteristics there are few synthesis methodologies for this class of heterocycles [17].
Our interest in the synthesis of such compounds was to shed some light on their biological study as antimicrobial agents as a part of our program aimed at the development of new heterocyclic compounds with potential biological activities [18].

Results and Discussion

Synthesis

Chalcones 1a–1c were synthesized by a base catalyzed Claisen-Schmidt condensation reaction [19] of appropriately substituted acetophenones and aldehydes. The method is attractive since it specifically generates the (E)-isomer. The IR spectra show the characteristic band for \( \text{C} = \text{O} \) at 1690–1695 cm\(^{-1}\), \( \text{C} = \text{C} \) Ar at 1598–1600 and 1450–1456 cm\(^{-1}\), while the vinyl \( \text{CH} = \text{CH} \) appeared at 1600 and 1475, while the vinyl \( \text{CH} = \text{CH} \) appeared at 1295–1300 cm\(^{-1}\). From \(^1\)H NMR spectra, all chalcones were geometrically pure and with trans-configuration \( (J_{\text{H}, \text{H}}) = 15.50–15.60 \text{ Hz} \). Saturation of the double bond or variation of the aliphatic part results in loss of the anti-inflammatory activity [20]. So, bromination of chalcones was carried out by adding bromine dropwise to the clear solution of 1a–1c in chloroform to afford the corresponding 2,3-dibromo-chalcones 2a–2c. Monobromo derivatives could be obtained from the corresponding dibromo-chalcones according to the method described by Holla et al. [21]. So, treatment of 2a–2c with dry benzene in the presence of triethylamine afforded 3a–3c (Scheme 1).

The pyrazole derivatives 4a–4c or 5a–5c were obtained by refluxing of dibromo-chalcones 2a–2c with phenylhydrazine or 2,4-dinitrophenylhydrazine in dry pyridine. The IR spectra of 4a–4c or 5a–5c showed the characteristic band for \( \text{C} = \text{N} \) at 1673–1680 and \( \text{C} = \text{C} \) Ar at 1598–1600 and 1450–1456 cm\(^{-1}\), while the \(^1\)H NMR spectra showed a singlet at 6.84–6.99 ppm for the pyrazole-H-4 (Scheme 2).

It has been reported that, \( \alpha, \beta \)-unsaturated ketones can react with hydrazine hydrate or phenylhydrazine to give the corresponding pyrazolines [22]. So, 1a–1c were treated with hydrazine hydrate or phenylhydrazine in ethanol to afford the \( \Delta^2 \)-pyrazolines.