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Synthesis and characterization of some chalcones and their cyclohexenone derivatives

Research Article

Thekke V. Sreevidya[1], Badiadka Narayana[1]*, Hemmige S. Yathirajan[2]

[1] *Department of Post-Graduate Studies and Research in Chemistry, Mangalore University, Mangalagangotri 574 199, INDIA*

[2] *Department of Studies in Chemistry, University of Mysore, Mysore 570 006, INDIA*

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Abstract: A series of chalcones and their derivatives have been synthesized. Chalcones, 1-(1,3-benzodioxol-5-yl)-3-(aryl)-prop-2-en-1-ones were prepared by the aldol condensation of 1-(1,3-benzodioxol-5-yl)ethanones and aryl aldehydes. Based-catalyzed condensation of 1-(1,3-benzodioxol-5-yl)-3-(aryl)prop-2-en-1-ones with ethyl acetoacetate yields corresponding ethyl 4-(1,3-benzodioxol-5-yl)-6-(aryl)-2-oxocyclohex-3-ene-1-carboxylates. Some of the synthesized chalcones were reported in the literature; the newly synthesized compounds were characterized by single crystal X-ray studies, IR, ^{1}H-NMR and LCMS mass spectral analysis.

Keywords: *Chalcones • Michael addition • Single crystal XRD • Cyclohexenones*

1. Introduction

Chalcones, one of the major classes of natural products with widespread occurrence in fruits, vegetables, spices, tea and soy-based foodstuff, have been recently the subject of extensive investigations due to their interesting pharmacological activities. Chemically they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system. It is a unique template molecule that is associated with several biological activities. The radical quenching properties of the phenolic groups present in many chalcones have raised interest in the use of the compounds or chalcone-rich plant extracts as either drugs or food preservatives [1]. Chalcones have been reported to possess many useful properties, including anti-inflammatory [2], antifungal [3-5], antioxidant [6], cytotoxic [7] and anticancer [8-11] activities. Certain chalcone derivatives are reported to inhibit the polymerization of tubulin to form microtubules and can be used as antimitotic agents [12-15]. Chalcone derivatives are also known to inhibit the destruction of myelin sheath in the central nervous system of multiple sclerosis patients and are thus useful in controlling the progressive nature of the disease [16]. Apart from being biologically important compounds, chalcone derivatives show non-linear optical (NLO) properties with excellent blue light transmittance and good crystallizability. Not only photonics deals with the synergy between optics and electronics, it also provides the ties between optical materials, devices and systems. The inventions of lasers and nonlinear optical phenomena (NLO) have opened up many new areas of devices and systems, like frequency conversion and optical switching, that are of practical interest to mankind [17]. The NLO effect in the organic molecules originates from a strong donor-acceptor intermolecular interaction, a delocalized π-electron system, and is also due to the ability to crystallize in non-centrosymmetric manner. Organic NLO materials are attracting a great deal of interest as they have greater optical susceptibilities, and higher optical thresholds for laser power compared to inorganic materials, as well as inherent ultrafast response times [18]. It is widely accepted that the NLO response is greatly increased upon lengthening of the chain of the conjugated π-bridge and chalcone derivatives have

* *E-mail: nbadiadka@yahoo.co.uk*

such a configuration, with two planar rings connected by a conjugated double bond and hence, show significant nonlinearity [19].

Many chalcones have been reported as having high antimalarial activity, probably as a result of Michael addition of nucleophilic species to the double bond of the enone [20,21]. Licochalcone A, isolated from Chinese liquorice roots, has been reported as highly effective in chloroquine resistant *Plasmodium falciparum* strains in a [3*H*] hypoxanthine uptake assay [22,23].

Michael addition reactions of chalcones and azachalcones with ethyl acetoacetate have been successfully performed in the presence of catalytic amount of K_2CO_3 and under high speed vibration milling conditions [24]. The reactions took place at ambient temperature, without any solvent, and were completed within a very short time. In most cases, conventional side reactions were avoided and thus high chemoselectivity and quantitative yields were achieved. The desired Michael adducts obtained consisted exclusively of two diastereomers, 'anti' and 'syn', which were determined and assigned by ^{1}H-NMR spectroscopy. Herein, we discuss the synthesis and characterization of two series of organic compounds, viz., chalcones and their cyclohexenone derivatives. Some of the chalcones were already reported in literature [25-28]. The newly synthesized compounds were characterized by elemental, IR, ^{1}H-NMR and LCMS mass spectral analysis; a few chalcones were characterized using single crystal XRD.

2. Experimental procedure

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds was confirmed by thin layer chromatography using Merck silica gel 60 F_{254} coated aluminium plates in petroleum ether/ethyl acetate medium. IR spectra were recorded on Shimadzu- FTIR Infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker (300 MHz) spectrometer using TMS as internal standard and mass spectra were recorded in LC/MSD Trap XCT spectrometer.

2.1. General procedure for the synthesis of chalcones (3a-n)

3',4'-Methylenedioxyacetophenone (0.01 mol) and substituted aryl aldehydes (0.01 mol) were dissolved in methanol (25 mL) and 5 mL of 10% KOH solution was slowly added to it under stirring at 15-20°C. Stirring continued for 2 h at the same temperature. Progress of the reaction was monitored by TLC. The precipitate was filtered off and washed with cold methanol. Recrystallization from methanol yielded the pure compounds with 62-89% yields.

Synthesis of chalcones can also be carried out using LiOH as a dual activation catalyst [25].

2.2. General procedure for the synthesis of ethyl 4-(1, 3-benzodioxol-5-yl)-2-oxo- 6-(aryl) cyclohex-3-ene-1-carboxylate (5a-i)

Chalcones and ethyl acetoacetate in the 1:1 ratio were refluxed in 15 mL of ethanol for 2 h in the presence of 0.5 mL 10% KOH. The reaction mixture was kept overnight at room temperature. The precipitate was filtered off and recrystallized from ethanol to yield the required material, as an isomeric mixture, with 58-78% yield.

2.3. Spectral data

2.3.1. Ethyl 4-(1,3-benzodioxol-5-yl)-6-(4-lorophenyl)-2-oxocyclohex-3-ene-1-carboxylate (5a)

IR (KBr, cm^{-1}): 1664 cm^{-1} ($\nu_{c=o}$ ketone), 1735 cm^{-1} ($\nu_{c=o}$ ester); ^{1}H-NMR (300 MHz): δ 1.06 (t, 3H, CH_3), 2.56-2.70 (m, 2H, -CH-CH-Ar), 3.23-3.41(m, 2H, CH_2-CH-Ar), 4.07- 4.14 (q, 2H, -OCH_2), 6.05 (s, 2H, -OCH_2O), 6.32 (s,1H, =CH), 6.89 (m, 3H, ArH), 7.31 (m, 4H, ArH); LCMS: 399 (M+1), 400 (M+2).

2.3.2. Ethyl 4-(1,3-benzodioxol-5-yl)-6-(3,4-dimethoxyphenyl)-2-oxocyclohex-3-ene-1-carboxylate (5b)

IR (KBr, cm-1): 1656 cm-1 (vc=o ketone), 1735 cm-1 (vc=o ester); 1H-NMR (300 MHz): δ 1.14 (t, 3H, CH3), 2.82-3.12 (m, 2H, -CH-CH-Ar), 3.56-3.68 (m, 2H, CH2-CH-Ar), 3.79 (s, 3H, OCH3), 3.82 (s, 3H, OCH3), 4.10- 4.16 (q, 2H, -OCH2), 6.08 (s, 2H, -OCH2O), 6.42 (s,1H, =CH), 6.74(d, 1H, ArH), 6.82 (m, 2H, ArH), 7.12 (m, 3H, ArH); LCMS: 425 (M+1), 426 (M+2).

2.3.3. Ethyl 4-(1,3-benzodioxol-5-yl)-6-(3-bromophenyl)-2-oxocyclohex-3-ene-1-carboxylate (5c)

IR (KBr, cm^{-1}): 1663 cm^{-1} ($\nu_{c=o}$ ketone), 1733 cm^{-1} ($\nu_{c=o}$ ester); ^{1}H-NMR (300 MHz): δ 1.10 (t, 3H, CH_3), 2.86-3.10 (m, 2H, -CH-CH-Ar), 3.71-3.82 (m, 2H, CH_2-CH-Ar), 4.07- 4.14 (q, 2H, -OCH_2), 6.04 (s, 2H, -OCH_2O), 6.49 (d,1H, ArH), 6.86 (d, 1H, ArH), 7.05 (d, 1H, ArH), 7.12 (m,1H, ArH), 7.26 (m, 2H, ArH), 7.44 (m, 1H, ArH), 7.49 (s,1H, =CH); LCMS: 445 (M+1), 446 (M+2).

2.3.4. Ethyl 4-(1,3-benzodioxol-5-yl)-6-(2-methoxynaphthalen-6-yl)-2-oxocyclohex-3-ene-1-carboxylate (5d)