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Structural analysis of two tetraketones and theoretical investigation of the reactions involved in their preparation

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ABSTRACT

The 2,2'-((5-(4-bromophenyl)furan-2-yl)methylene) *bis* (5,5-dimethylcyclohexane-1,3-dione) (**3**) and 2,2'-((5-(4-chlorophenyl)furan-2-yl)methylene) *bis* (5,5-dimethylcyclohexane-1,3-dione) (**4**) were prepared in, respectively, 63% and 59% yield, *via* $ZrOCl_2 \cdot 8H_2O$ catalyzed condensation reactions between dimedone and appropriate aldehydes. Their structures were investigated by IR, NMR, and X-ray spectroscopy techniques. The asymmetric unit of tetraketone **3** is composed of just one molecule, while two almost identical crystallographically independent molecules of compound **4** are present there. Compound **3** is conformationally similar to both molecules of **4**. The diketone rings assume a half-chair conformation with the flaps oriented toward the same side of the substituent at C1. Each diketone ring is featured by an electronic delocalization path encompassed through the keto-enol moiety. All bond lengths inside this conjugated system are intermediate between those of pure double and single bonds. Furthermore, the furan plane of the substituent at C1 is almost parallel to the bond axes bridging the diketone rings as a consequence of steric hindrance effects between the heterocycle moiety and two hydrogen bonded oxygens. The enol forms of compounds **3** and **4** were noticed *via* IR and NMR spectroscopies. Furthermore, thermodynamics parameters were calculated in order to interpret the experimental results. In this line, theoretical findings reveal that electronic and solvent effects play an important role in the chemical reactions involved in the preparation of tetraketones.

1. Introduction

The tetraketones **(I)** are important intermediates that can be used as versatile precursors in the synthesis of tricyclic heterocycles such as xanthenodiones **(II)**, acridindiones **(III)** [1], benzopyrans **(IV)** and thioxanthenes **(V)** [2] (Scheme 1). All of these heterocycles exhibit important biological activities. In addition, tetraketones are known for their antioxidant properties [3] and the strong potential for repairing inflammation and asthma [4]. These compounds also have significant lipoxygenases [3,5], tyrosinase [6,7] and protein kinases inhibitory activity [8].

In general, the tetraketones can be prepared *via* Knoevenagel condensation and Michael addition of aldehydes with cyclic 1,3-diketones, with or without the use of catalysts. Because of their synthetic utility and biological activities, various synthetic methodologies have been developed for the preparation of this class of compounds. However, many of these methods utilize toxic solvents and high catalyst loading, present long reaction times, require high temperatures, afford tetraketones in low yields, and involve laborious workup procedures [9]. In this paper, we describe an alternative methodology for preparation of tetraketones *via* $ZrOCl_2 \cdot 8H_2O$ catalyzed reactions between dimedone and aromatic aldehydes. We also describe the results of X-ray, NMR and IR investigations of the synthesized tetraketones. Theoretical calculations concerning these compounds and the reactions involving them are also presented.

2. Experimental

2.1. Generalities

All reagents were purchased from commercial sources (Sigma-

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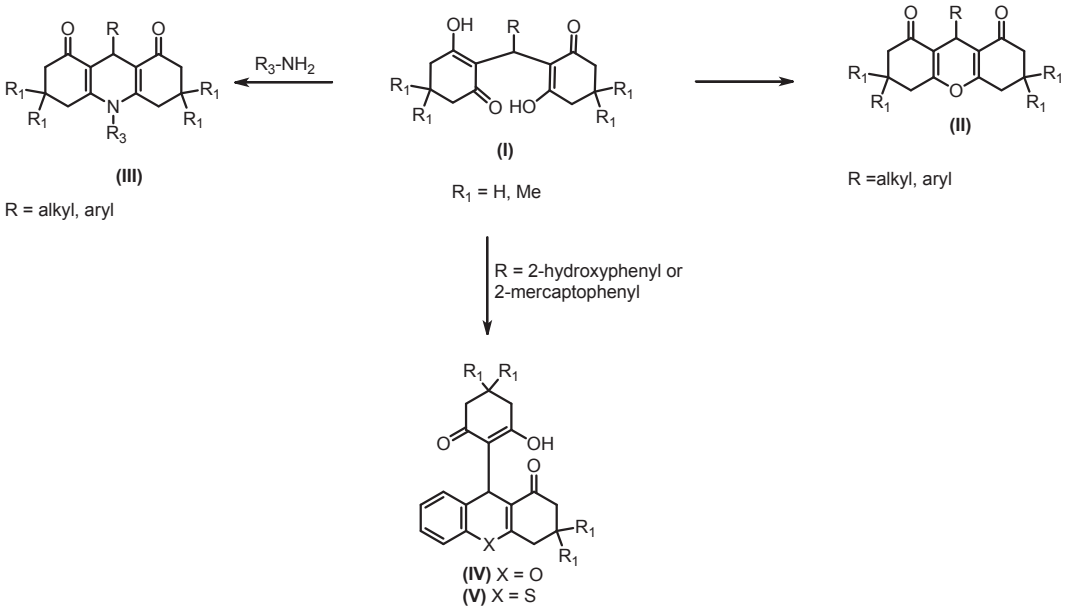

Scheme 1. The general structures of tetraketones (**I**) and derivatives (**II**)–(**V**).

Aldrich - St. Louis, MO, US and Vetec - Rio de Janeiro, Brazil) and were employed as received. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 instrument (300 MHz and 75 MHz, respectively), using deuterated chloroform as solvent. Hydrogen nuclear magnetic resonance (NMR) data are presented as follows: chemical shift (δ) in ppm, the number of hydrogen atoms, multiplicity, J values in Hertz (Hz). Multiplicities are shown as the following abbreviations: s (singlet), d (doublet), m (multiplet). Infrared spectra (IR) were obtained on a Varian 660-IR equipment with accessory GladiATR. The exact mass of the compounds was determined on micrOTOF QII® (Bruker Daltonis, Germany) equipped with a microESI (Electrospray) ionization source. The compounds were dissolved in acetonitrile (100% LCMS) and acidified with 0.1% formic acid. The mass was acquired in positive mode scanning from 50 to 1000 Da. Melting points were determined using MQAPF-301 melting point apparatus (Microquimica, Santa Catarina, Brazil) and they were not corrected.

2.2. Synthesis

2.2.1. Synthesis of 2,2'-((5-(4-bromophenyl)furan-2-yl)methylene) bis (5,5-dimethylcyclohexane-1,3-dione) (3)

In a typical procedure, a round-bottomed flask (25 mL) was charged with 2 mmol of 5,5-dimethylcyclohexan-1,3-dione (295 mg, 2.00 mmol), 5-(4-bromophenyl) furan-2-carbaldehyde (258 mg, 1.00 mmol) and $ZrOCl_2 \cdot 8H_2O$ (12 mg, 2 mol %). The mixture was stirred at 85 °C and after 10 min of reaction, 100 μL of distilled water were added. The progress of the reaction was monitored by TLC analysis and it took 2 h for its completion. Then, the mixture was cooled to room temperature. Thereafter, 50 mL of dichloromethane were added to the flask and the mixture was maintained under stirring. The catalyst, which is insoluble in dichloromethane, was separated by filtration. After that, 50 mL of ethanol was added to the filtrate and the system was kept undisturbed for the crystallization process. This procedure afforded compound **3** as yellow solid in 63% yield (321 mg, 0.630 mmol). Crystals suitable for X-ray diffraction studies were obtained from the above-mentioned crystallization procedure. The obtained crystals were thoroughly washed with cold ethanol and dried. The structure of **3** is supported by the following data.

Yellow solid. Mp 159–161 °C. IR (ATR) ν_{max}/cm^{-1}: 2962, 2870, 1588, 1538, 1370, 1165, 1147 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.24 (1H, s, OH), 7.42 (2H, d, J = 8.2 Hz), 7.36 (2H, d, J = 8.2 Hz), 6.55 (1H, s), 6.02 (1H, s), 5.46 (1H, s), 2.39 (4H, s), 2.33 (4H,s), 1.22 (6H, s), 1.11 (6H, s).^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.7, 189.4, 151.9, 151.4, 131.6, 129.9, 124.8, 120.4, 114.0, 108.8, 106.4, 46.9, 46.2, 31.3, 29.9, 29.3, 26.4. HRMS m/z ($M + H^+$): Calculated for $C_{27}H_{30}BrO_5$, 513.1277. Found: 513.1308.

Compound **4** was obtained in 59% yield using a similar procedure to that described for the preparation of **3**. The reaction involved in the preparation of **4** took 2 h and 15 min for its completion. The structure of **4** is supported by the following data.

2.2.2. 2,2'-((5-(4-chlorophenyl)furan-2-yl)methylene) bis (5,5-dimethylcyclohexane-1,3-dione) (4)

Yellow solid. Mp = 164–166 °C. IR (ATR) ν_{max}/cm^{-1}: 2953, 2871, 1580, 1534, 1372, 1167, 1150 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.24 (1H, s, OH), 7.42 (2H, d, J = 8.2 Hz), 7.27 (2H, d, J = 8.2 Hz), 6.55 (1H, s), 6.02 (1H, s), 5.46 (1H, s), 2.39 (4H, s), 2.33 (4H, s), 1.22 (6H, s), 1.11 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.7, 189.4, 151.9, 151.4, 132.3, 129.5, 128.7, 124.5, 114.0, 108.8, 106.4, 46.9, 46.2, 31.3, 29.9, 29.3, 26.4. HRMS m/z ($M + H^+$): Calculated for $C_{27}H_{30}ClO_5$, 469.1782. Found: 469.1806.

2.3. X-ray diffraction analysis

Prism-shaped single crystals of tetraketones **3** and **4** were selected and mounted, at room temperature, on a κ-goniostat (Bruker-AXS Kappa Duo diffractometer) and exposed to X-ray beam (Mo Kα, λ = 0.71073 Å). X-Ray diffraction intensity data were recorded using an APEX II CCD detector. Data collection strategy was set with φ scans and ω scans with κ offsets using the APEX2 software [10]. Other crystallographic softwares were used as follows: SAINT [10] (indexing, integration and scaling of raw data), SHELXS-97 [11] (structure solving using Direct Methods), SHELXL-97 [11] (structure refinement by full-matrix least squares method on F^2) and MERCURY [12] (structure analysis and graphical