

Investigación

Rhodium (II) Catalyzed Wolff Rearrangement of a Carbenoid Derived from an Indolyl Diazopropanedione

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Abstract. The Rhodium (II) acetate catalyzed reaction of 3-diazo-1-(indol-3-yl)-propane-1,2-dione did not give the expected intramolecular cyclization product, affording only 3-acetylindole in 70% yield. A reaction mechanism which involves a Wolff rearrangement is proposed.

Key Words: Carbenoid, rearrangement, indole.

Resumen. La reacción catalizada por acetato de rodio (II) de la 3-diazo-1-(3-indolil)-1,2-propanodiona no dio el producto de ciclación intramolecular esperado, generando solamente 3-acetilindol en un rendimiento del 70%. Se propone un mecanismo de reacción que involucra una transposición de Wolff.

Palabras Clave: Carbenoide, transposición, indol.

Introduction

The diazo group chemistry has taken a new interest as a consequence of the development of catalytic methods with transition metals which particularly convert diazoketones in to valuable tools in organic synthesis with several applications in homologations, X-H bond insertions, ylide formations, and reactions with alkenes and aromatic compounds [1].

The carbenoid reactions over rich-electron heterocyclic compounds have been useful in the synthesis of polyenes from furans [2] and in the indolizidine alkaloids synthesis from pyrroles [3].

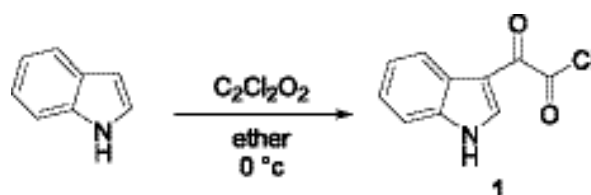
Even though, the first reactions of carbenoids derived from α -diazoketo compounds and copper bronzes over indoles were described almost 70 years ago [4], however these reactions were of limited scope and only ethyl diazoacetate or diazoacetone were used as carbenoid precursors, while the yields were moderate or low [5,6]. This perspective changed when rhodium (II) carboxylates were introduced and catalytic processes were performed. Thus, intermolecular carbenoid insertions on indoles were used by the Muthusamy [7] and Kerr's [8] groups to prepare several 3- and 2- substituted indoles. Additionally, there are many reports on the intramolecular carbenoid insertion and subsequent cyclization of diazoalkanoylindoles wherein the side chain is appended at the nitrogen position [9], and at the C-2 [10], C-3 [11] and C-4 [12] positions of indole.

In connection with other synthetic studies, we believed that carbenoid intramolecular insertions on indole could be used in the syntheses of biologically active substances, particularly in the synthesis of Nostodione A, a potent mitotic spindle poison from a blue-green alga *Nostoc commune* [13]. Nevertheless, we found in this way a collateral reaction which does not have precedent in the indole moiety that occurs

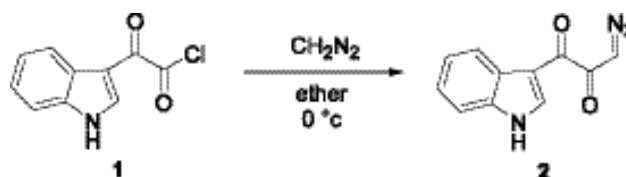
instead of the carbenoid insertion. Therefore, this is the first report on a Wolff type rearrangement in carbenoids derived from 3-diazoalkanoylindoles.

Results and discussion

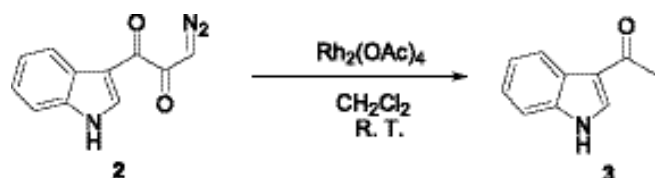
Initially we prepared the indoleglyoxylic acid chloride **1** by addition of an ethereal solution of indole into an ethereal solution of oxalyl chloride in a modification of the procedures reported by the Armstrong [14] and Lings [15] research groups, in quantitative yield.



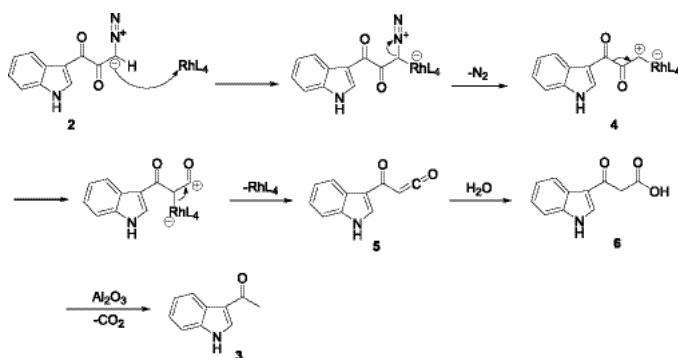
The next step in the synthetic route consisted on the treatment of compound **1** with an excess of ethereal diazomethane (3:1) at 0 °C to afford the 3-diazo-1-(indol-3-yl)-propane-1,2-dione (**2**) in 97 % yield [15, 16].



Finally, exposure of diazoketone **2** to a catalytic amount of rhodium (II) acetate in dichloromethane solution at room temperature afforded after alumina column chromatography purification, the unexpected 3-acetylindole **3** as the only isolable product in 70% yield.



Mechanistically, one can rationalize the 3-acetylindole formation as a consecutive Wolff rearrangement-carbon dioxide extrusion process, such as scheme 4 summarizes. In the first step the catalyst electrophilic addition causes the loss of molecular nitrogen and the production of a metal stabilized carbene (**4**). The subsequent Wolff rearrangement from carbenoid **4** to ketene **5** has preceding reports in other aliphatic and aromatic diazoketones [17-20]. However, at the moment indolyl diazoketones have not been reported. Once ketene **5** has been formed, reaction with water from alumina (grade III activity) used in the purification gives the β -ketoacid **6** which rapidly generates carbon dioxide and 3-acetylindole. Similar decarboxylation reactions were reported by Meier, *et al.* [21] in some 2-diazo-1,3-dicarbonyl compounds. In addition, β -ketoacids can be decarboxylated in slight acid conditions [22-25].



In conclusion, we proposed a mechanism that involves a Wolff rearrangement to explain the formation of 3-acetylindole from 3-diazo-1-(indol-3-yl)-propane-1,2-dione (**2**). We are currently performing further experiments in order to elucidate the mechanistic details that would help us to predict the course of these carbenoid reactions.

Experimental

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Solvents were

distilled before use, ether and tetrahydrofuran (THF) were dried over sodium using benzophenone as indicator. Diazomethane was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) using a minimum amount of water and ethanol as cosolvent, and dried over KOH pellets before use. Silica gel (230-400 mesh) and neutral alumina were purchased from Merck. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Fisher-Johns melting point apparatus and they are uncorrected. ^1H and ^{13}C NMR spectra were recorded using a Varian Gemini 200, the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a JEOL JMS-5X 10217 in the EI mode, 70 eV, 200 °C via direct inlet probe. Only the molecular and parent ions (m/z) are reported. IR spectra were recorded on a Nicolet Magna 55-X FT instrument.

Indol-3-yl-oxoacetyl chloride (1). To a stirred solution of indole (0.5 g, 4.2 mmol) in anhydrous ether (35 mL), at 0 °C, oxalyl chloride (0.41 mL, 0.59 g, 4.7 mmol) was added dropwise during 30 min; stirring and cooling were continued for 1 hr. more. The resulting yellow crystals of **1** (0.97 g, 100% yield), were collected on a filter, washed with anhydrous ether, and dried *in vacuo* over potassium hydroxide; mp 134 °C (lit. 134-136 °C) [14, 15].

3-diazo-1-(indol-3-yl)-propane-1,2-dione (2). An ice-cold solution of the acid chloride **1** (0.207g, 1 mmol) in freshly distilled ether (5 mL) was treated with then an ether solution of diazomethane (3 mmol) from *N*-methyl-*N*-nitroso-4-toluenesulfonamide at 0 °C under a nitrogen atmosphere. A vigorous evolution of nitrogen occurred, and the mixture was allowed to warm to room temperature overnight. The solvent was removed *in vacuo* and the product was purified by column chromatography (Al_2O_3 , hexane/ethyl acetate 9:1), to afford a yellow solid (0.21 g, 97%); mp 145 °C, IR (film) ν_{max} 3456, 3126, 2113, 1628 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 6.33 (s, 1H), 7.25-7.45 (m, 2H), 8.42 (m, 2H), 8.73(d, 1H), 9.15 (s, 1H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 54.5, 111.7, 122.4, 123.4, 124.3, 126.4, 134.3, 135.8, 137.2, 172.5, 185.7; MS [EI+] m/z : 213 [M]⁺ (15), 144 [$\text{M} - \text{COCHN}_2$]⁺ (100).

Reaction of 3-diazo-1-(indol-3-yl)-propane-1,2-dione (2) with rhodium (II) acetate. A solution of the diazopropanedione **2** (0.214 g, 1 mmol) in dry CH_2Cl_2 (10 mL) was stirred with $\text{Rh}_2(\text{OAc})_4$ (2 mg) under nitrogen atmosphere at room temperature. After 2 h, the mixture was evaporated *in vacuo* and purified by column chromatography (Al_2O_3 , activity III, hexane/ethyl acetate 8:2) to yield 3-acetylindole **3** (0.111 g, 70%); mp 189-190 °C. IR (CHCl_3). ν_{max} 3463, 1649 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 2.48 (s, 3H), 7.19 (m, 4H), 7.99 (m, 1H), 9.01 (s, 1H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 26.8, 111.5, 116.7, 121.2, 121.3, 122.3, 125.0, 132.7, 136.4, 192.3; MS [EI+] m/z (%): 159 [M]⁺ (50), 144 [$\text{M} - \text{CH}_3$]⁺ (100).

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