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Expedited Baeyer–Villiger oxidation of steroidal ketones by microwave irradiation

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ABSTRACT

Microwave (MW) assisted reactions are currently having considerable importance in the synthesis of organic compounds. Considering the remarkable application of Baeyer–Villiger (BV) reaction in the synthesis of natural products and steroid–peptide conjugates, we report here some of our findings of BV oxidation of carbonyl compounds with special reference to steroidal ketones under MW irradiation justifying its accelerating effect.

1. Introduction

The Baeyer–Villiger (BV) oxidation is an important reaction in organic synthesis which leads to the conversion of acylic ketones into esters and cyclic ketones into lactones [1]. Diverse experimental and theoretical studies aiming to know insights on the mechanistic details of this reaction have been well documented in chemical literature [2–10] in recent times. In fact the reaction finds a remarkable application on the synthesis of natural product compounds and their analogs [2,5]. In the steroid field the role of BV reaction for converting 20-oxopregnanes to 17-acetoxysteroids of potent sex hormones [11], and also of the formation of the biologically active steroidal D-ring lactones are well documented in literature [12–17]. This in conjugation with our interest on steroid transformations [18–23], we initiated the work on the development of steroid–peptide conjugates which are currently gaining importance because of their potent biological importance as synthetic receptors of oligopeptide sequences [24], as protease-like artificial enzymes [25] and as mimics of natural cationic peptide antibiotics [26]. Thus in connection with that work on a steroid–peptide conjugate synthesis, we did require to perform BV oxidation as the key step on the compound 5α-pregnan-3,17-dione **1**, to get a *seco*-steroidal building block via its lactonization and subsequent ring opening to *seco*-steroidal hydroxysteroids to incorporate a peptide bond with it. Usual BV oxidation of the compound **1** with *m*-CPBA or perbenzoic acid in presence or in absence of a catalyst like CAN [27], H_2SO_4 [28], TFA [29] took much longer time and many times the reaction mixture had to be kept for 2–3 weeks in dark for completion. Sometimes reaction gave a mixture of products because of the incomplete oxidation at both the sites of the carbonyl groups of the compound **1** simultaneously, which drew our attention towards the application of MW irradiation in BV oxidation of the compound. Moreover reaction time did not get reduced when reactions were performed on refluxing chloroform, rather they became messy giving number of products.

The most fundamental obstacles in developing technologies are to minimize the energy consumption and to eliminate/minimize the use of hazardous substances. In this scenario, use of microwave energy to bring about chemical transformations is a suitable alternative, as it takes care of two very essential criteria of synthesis: minimize energy consumption required for heating and time required for the reaction [30]. Therefore, currently studies on the effect of MW irradiation in organic and macromolecular chemistry are a subject of considerable interest [31,32]. Accelerating effect and efficient non-contact heating are some of the traits of MW irradiated reactions. Recently Carsten et al. [33], in their work on polymer chemistry, demonstrated the accelerating effect of MW irradiation through the facile synthesis of two higher lactones, viz., 1-oxa-2-oxocyclooctanone and 1-oxo-2-oxacyclononanone via BV reaction of their corresponding ketone precursors. This has led us to hit upon the idea of applying MW technology in BV oxidation of compound **1** to get the desired steroidal ring-A lactone.

Thus when the compound **1** was subjected to BV oxidation under MW irradiation at 350W, in chloroform, it furnished the oxidized products 3-oxa-4-oxo-4a-homo lactone **1a** (60%) and 3-oxo-4-oxa-4a-homo lactone **1b** (40%) in a very clean and fast reaction. Obviously oxidation occurred simultaneously at the sites of both the carbonyl groups of the compound 5α-pregnan-3,

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