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Regioselective hypervalent iodine-induced Favorskii rearrangement of 3-oxo-5β-steroids

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ABSTRACT

Treatment of 3-oxo-5β-steroids with diacetoxyiodobenzene/KOH triggered a fast and regioselective Favorskii rearrangement that exclusively led to 3β-methoxycarbonyl-5β-4-norsteroids in good yields. The outcome of the reaction indicates that although both Cyclopropanone and Semi-benzylic pathways are possible, in the case of 3-oxo-5β-steroids, only the last participates. Unambiguous characterization of the products was achieved by NMR and X-ray Diffraction studies.

1. Introduction

Hypervalent iodine compounds have been established as useful tools in organic chemistry [1–8]. In particular, the electrophilic character of the hypervalent iodine moiety combined with its ability as leaving group, allow its introduction followed by a nucleophilic displacement in a tandem process that has been particularly useful in the α-functionalization of aldehydes, ketones and carboxylic acids.

The Favorskii rearrangement, (FR) originally reported by the Russian chemist Aleksei E. Favorskii [9] is a well known structural transformation that takes place when ketones bearing a good leaving group **(X)** at the α-position are treated with a nucleophilic base to produce esters, amides or carboxylic acids depending on the conditions [10,11]. Although several mechanisms have been postulated [10], evidences have been used to discard most of them, leaving the Cyclopropanone (CPM) and Semibenzylic (SBM) mechanisms as the generally accepted pathways (Scheme 1).

CPM as postulated by Loftfield [12,13] can only operate when a proton from the α′position to the carbonyl group can be abstracted by a base, leading to an enol that displaces the leaving group through a S_NI reaction that leads to the cyclopropanone intermediate. Nucleophilic addition to the carbonyl group followed by rearrangement leads to products. In the case of unsymmetrically substituted ketones, the two possible regioisomers are produced.

When the absence of α′-protons precludes the formation of the cyclopropanone intermediate, the rearrangement can only occur through the Semi-Benzylic Mechanism (SBM) [14] in which the nucleophilic addition to the carbonyl group leads to an intermediate that can only rearrange to a single regioisomer. Consequently, the occurrence of two regioisomers is an evidence of the participation of CPM, but although the presence of α′-protons is mandatory for the occurrence of CPM, this does not rule out the mixed participation of SBM. On the other hand, the exceptional occurrence of a single regioisomer in FR of compounds bearing α′-protons, suggests the exclusive participation of SBM.

Despite of the profuse application of FR [10,11], only few studies on the hypervalent iodine-induced Favorskii ring contraction of cyclic ketones have been described. Moriarty reported that treatment of 5α-cholestan-3-one **(1)** with diacetoxyiodobenzene (DIB) and KOH in CH_3OH produces a mixture of the 4-norcholestanes **2a** and **2b** (Scheme 2, Eq. 1) [15]. We recently described that reactions of 23-oxoepismilagenin acetate **(3)** or hecogenin acetate **(5)** with DIB and KOH in CH_3OH produce the corresponding ring contraction derivatives (Scheme 2, Eqs. 2 and 3) [16,17].

Although in Eq. 1, the formation of the major product **2a** was interpreted as a result of the SBM [15], the participation of CPM must be also considered, because **2b** can only arise from this pathway. Provided that **2a** can be produced by both, the CPM and the SBM, the 9/1 ratio in which **2a** predominates over **2b**, suggests that

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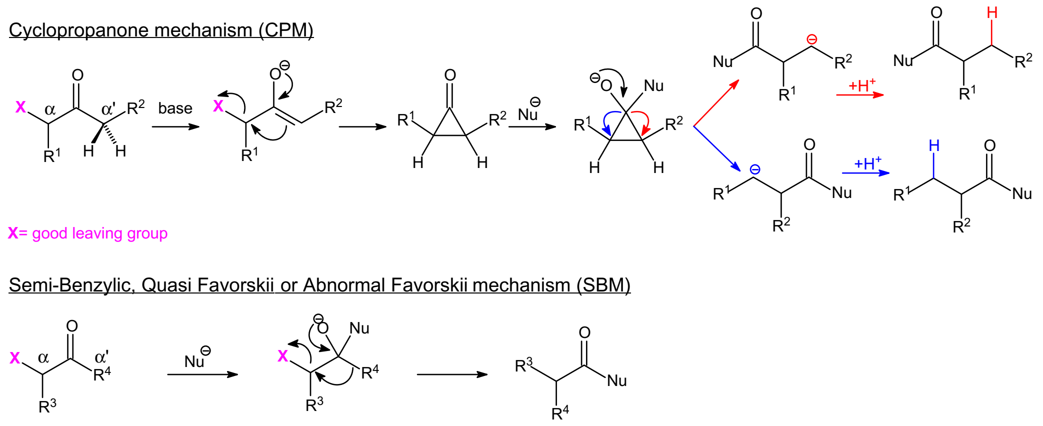
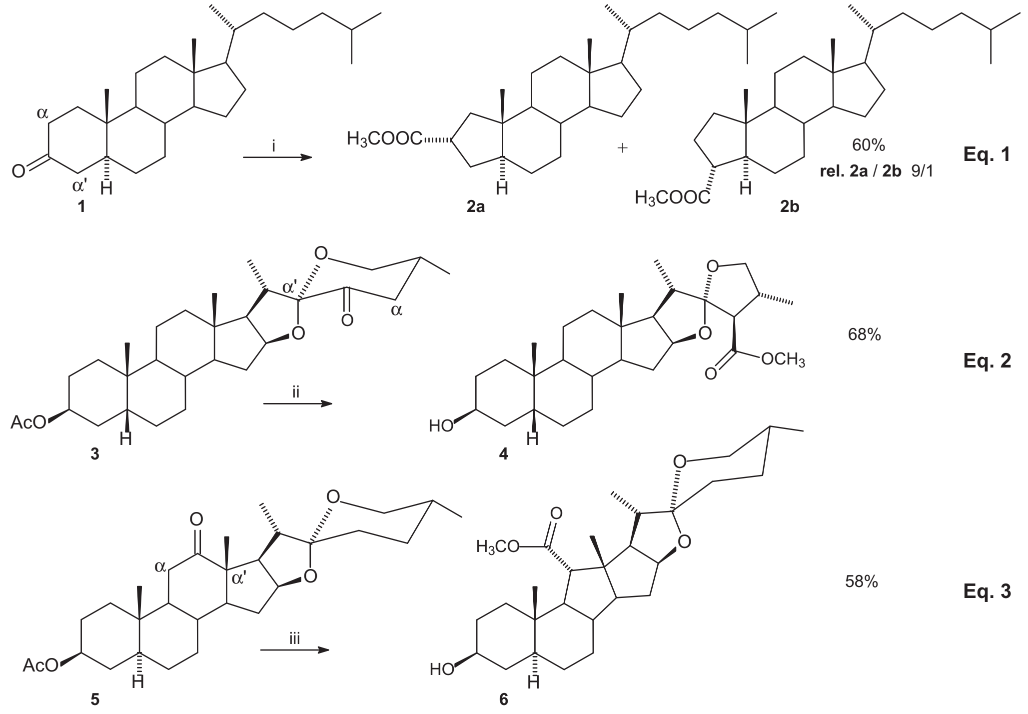


Scheme 1. Cyclopropanone and Semibenzylic mechanisms for Favorskii rearrangement.



i) KOH/ DIB in CH_3OH/THF, R.T., ii) KOH/ DIB in CH_3OH, R.T. iii) KOH/ DIB in CH_3OH, reflux.

Scheme 2. Hypervalent iodine induced Favorskii rearrangement of steroid ketones.

in this particular case both mechanisms occur simultaneously, although SBM predominates. On the other hand, the absence of α′-protons in compounds **3** and **5** (Eqs. 2 and 3), makes the exclusive participation of SBM mandatory and justifies the observed regioselectivity [16,17].

Examination of the literature indicates that when iodine III compounds are employed, FR of cyclic ketones is only a deviation of the more generally observed α-hydroxylation-ketalization course (Scheme 3, Eq. 4) [18]. Daum described that treatment of 17β-hydroxy-19-nor-5α-androstan-3-one **(9)** with DIB/KOH in CH_3OH led to a mixture of the 2α-hydroxy-3,3-dimethoxy ketal **10** as major product and only one the two possible regiosomers **(11)** resulting from A-ring contraction, (Scheme 3, Eq. 5) [19]. Additionally the same treatment of the ketone **12**, led to the α-hydroxyketal **13** as the sole product [20].

The above-mentioned results indicate that steric hindrance plays a crucial role in the reaction pathway leading to Favorkii rearrangement in sterically hindered systems, rather than the α-funtionalization observed in the less hindered partners. This prompted us to explore the reactivity of the hindered 5β-3-oxo-steroids through the DIB/KOH couple. Herein we report on the regioselective hypervalent iodine-induced Favorskii rearrangement of 5β-3-oxo-steroids and the unambiguous characterization of the products of the studied transformation.

2. Experimental section

2.1. General

Reactions were monitored by TLC on ALUGRAM® SIL G/UV254 plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1% solution of vanillin in 50% $HClO_4$ and heated until color developed. Melting points were measured on a