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The catalytic tandem oxidation/benzilic ester rearrangement (BER): insights into reaction mechanism and stereoselectivity

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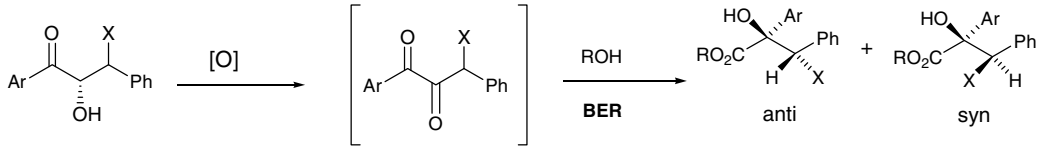
Abstract—This Letter describes an expeditious regiospecific and stereoselective approach to tertiary α-hydroxyesters via a simple one pot tandem catalytic oxidation/benzilic ester rearrangement of acyclic α-hydroxyketone substrates. Mechanistic studies confirming the regioselective nature of this reaction are discussed, including some insights into the nature of the stereoselectivity encountered in this reaction.

The benzilic acid rearrangement (BAR) was discovered by Liebig in 1838[1] and since then both this (hydroxide = nucleophile) and the analogous benzilic ester rearrangement (BER) (alkoxide = nucleophile) has been the subject of a plethora of experimental and theoretical studies over the last 50 years.[2,3] This 1,2-rearrangement has been applied to the synthesis of a number of important compounds.[4–6] For cyclic systems it is quite useful from a synthetic point in that, like such rearrangements as the Favorskii rearrangement, it leads to ring contracted products.

As an approach to the creation of the tertiary α-hydroxy ester functionality, a unit which is present in a plethora of biologically active compounds like, oxybutynin[7] and topotecan,[8] we have recently introduced a simple highly efficient strategy based on the tandem stoichiometric oxidation/benzilic ester rearrangement of α-hydroxyketone substrates (Scheme 1).[9] We have shown that α-hydroxyketone substrates are readily oxidised in situ to intermediate α-diketones (this was confirmed by the isolation of a quinoxaline adduct upon adding 1,2-diaminobenzene to the reaction mixture[9]) which subsequently undergo stereoselective benzilic ester rearrangements affording tertiary α-hydroxy ester diastereomers when attacked by an appropriate nucleophile (e.g., methoxide or ethoxide, etc.). As far as we are aware, studies on the stereoselectivity of this rearrangement in acyclic systems are quite rare.

In this Letter we report our very recent findings on the results of an experiment verifying the exclusive



Scheme 1.

Keywords: Benzilic acid rearrangment; Benzilic ester rearrangment; Isotopic label; Regioselectivity; Diastereoselectivity.
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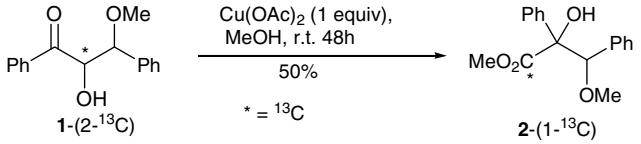
migration of only one group during the BER and on the development of a stereoselective catalytic version of this reaction.

We became curious to know which of the groups present in the α-diketone intermediate; the aryl group or the α-substituted benzyl group (Scheme 1), migrated preferentially. A number of decades ago Collins and Neville carried out an elegant experimental study using a radioactive labelled precursor to show that in the case of the hydroxide promoted BAR of 1,3-diphenylpropan-1,2-dione it was the benzyl group that migrated preferentially.[10] Given the difference between our system (a BER having an α-substituted benzyl group in the putative α-diketone intermediate) and the Collins/Neville system, we decided to carry out the following study to determine if our BER was completely regiospecific.

We prepared 1,3-diphenyl-2(^{13}C)-hydroxy-3-methoxypropan-1-one **1**-(2-^{13}C) (this existed as a mixture of diastereomers) from ^{13}*C*-methyl acetophenone[11] using our previously reported method.[9] Labelled hydroxyl ketone **1**-(2-^{13}C) was then subjected to our oxidation/BER protocol giving the corresponding ester diastereomers **2**-(1-^{13}C) in 50% yield (Scheme 2).

Analysis of this mixture of diastereomers by ^{13}C NMR spectroscopy showed conclusively that the ^{13}C label had been incorporated into the ester carbonyl function (two very intense peaks were observed at 174 and 173 ppm, respectively). This was also supported by the ^{1}H NMR spectrum when the methyl ester protons of each hydroxyester diastereomer furnished a doublet, due to long-range coupling with the carbonyl ^{13}C atom. The coupling constant for the major isomer was 6 Hz, whilst the minor isomer had a coupling constant of 3 Hz. In the case of either diastereomer there was no

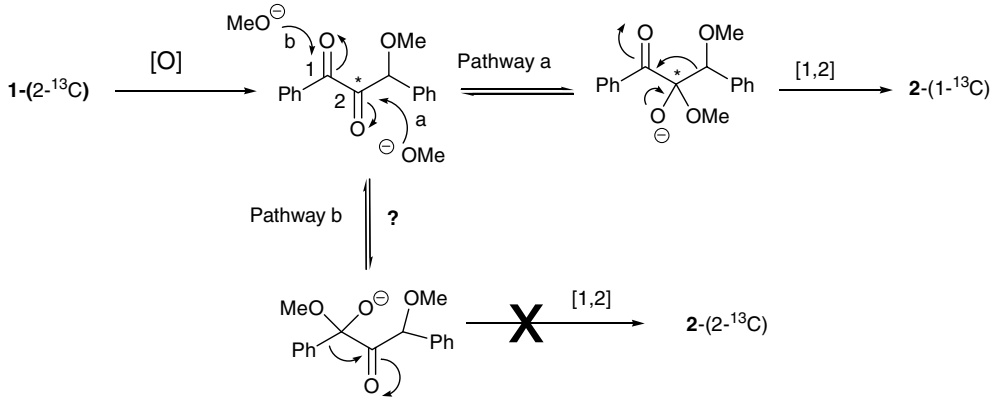


Scheme 2.

enhancement in the signals for C-2 (87.64 and 86.24 ppm). This result confirms that the CH(OMe)Ph group exclusively migrates in this rearrangement (Scheme 3, pathway a). The fact that no **2**-(2-^{13}C) ester diastereomers were obtained from the reaction might indicate that there was no attack on the carbonyl carbon-1 (Scheme 3, pathway b). However, this result does not eliminate the possibility of reversible attack of the nucleophile at the carbonyl carbon-1 without migration of the phenyl group. On the basis of the hard and soft acid and base principle (HSAB) of Pearson, selective attack at carbonyl carbon-2 would be expected.[12] Assuming that carbonyl-1 spends most of its time coplanar and conjugated with both the phenyl group and with carbonyl-2, then it is anticipated that carbonyl carbon-1 should be a softer centre than carbonyl carbon-2. As methoxide is categorised as a hard base,[12] it would be expected on the basis of the HSAB theory that this nucleophile would have a greater preference for carbonyl-2 and thus preferentially attack this site. Studies are currently underway at addressing this issue.

With the objective of making this procedure even more efficient, we decided to use catalytic quantities of Cu(II).[13] Thus we conducted a set of preliminary experiments to probe the catalytic nature of this procedure. We chose the α-hydroxyketone **3** as our substrate, which gives the tertiary α-hydroxy ester **4** as a mixture of *anti*-**4a** and *syn*-**4b** (Table 1). We started the experiment with 1 equiv of $Cu(OAc)_2$ and gradually decreased the loading of this oxidant (Table 1). The reactions were run in methanol at room temperature for 48 h.[14] These results were very encouraging and showed that under these conditions it was possible to use as little as 5 mol % $Cu(OAc)_2$ to get full conversion of the α-hydroxyketone substrate **3** to the ester diastereomers **4a** and **4b** (Table 1, entry 5). At a loading level of 1 mol % $Cu(OAc)_2$ some substrate was found to be present. The best yield was obtained under these conditions using 10 mol % $Cu(OAc)_2$.

Some comments need to be made regarding the diastereoselectivity of this reaction. The principle trend was that the diastereoselectivity seemed to increase as the quantity of catalyst was reduced. From 100 mol % (entry 1) to 1 mol % (entry 6) the diastereoselectivity doubled,



Scheme 3.