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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7957–7960

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

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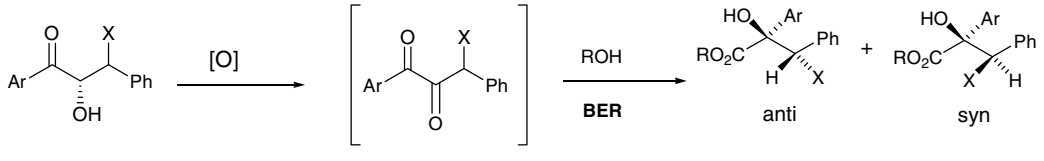
Received 7 July 2007; revised 16 August 2007; accepted 10 September 2007
Available online 14 September 2007

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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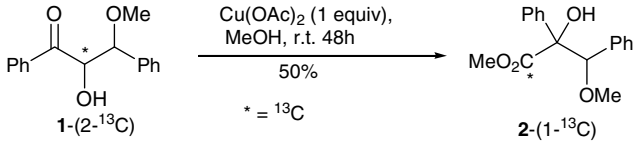
doi:10.1016/j.tetlet.2007.09.066

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

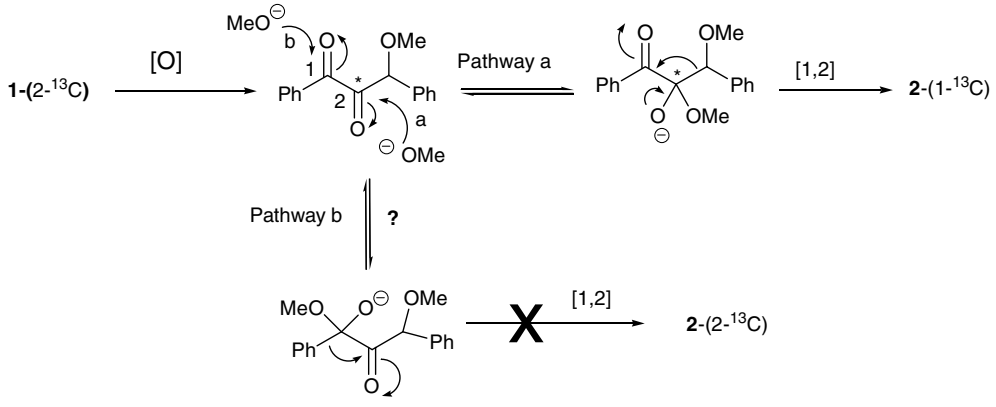


Scheme 2.

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.

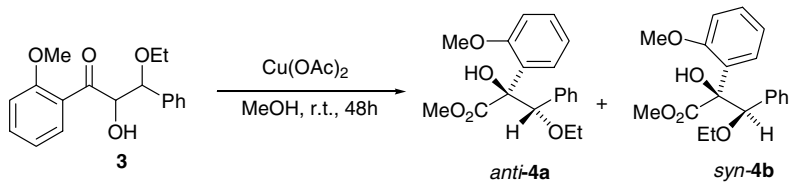
With the objective of making this procedure even more efficient, we decided to use catalytic quantities of Cu(II).[13] Thus we conducted a set of preliminary experiments to probe the catalytic nature of this procedure. We chose the α-hydroxyketone **3** as our substrate, which gives the tertiary α-hydroxy 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.

Table 1.

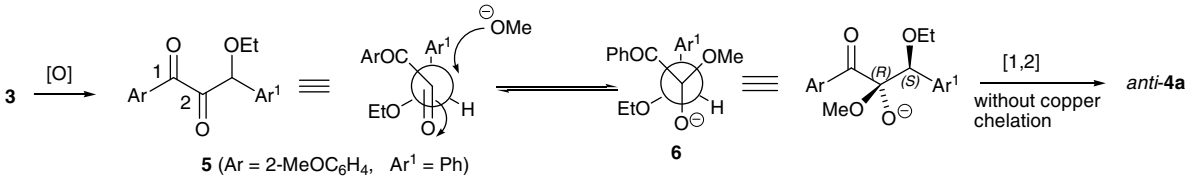


Entry	Substrate (mmol)	$Cu(OAc)_2$ (mol %)	Yield (%)	*anti*-**4a**:*syn*-**4b**[a]
1	0.47	100	70	2.1:1
2	0.33	50	75	2.7:1
3	0.13	25	74	3.6:1
4	0.5	10	87	4.5:1
5	0.13	5	73	4.6:1
6	0.13	1	67[b]	4.2:1

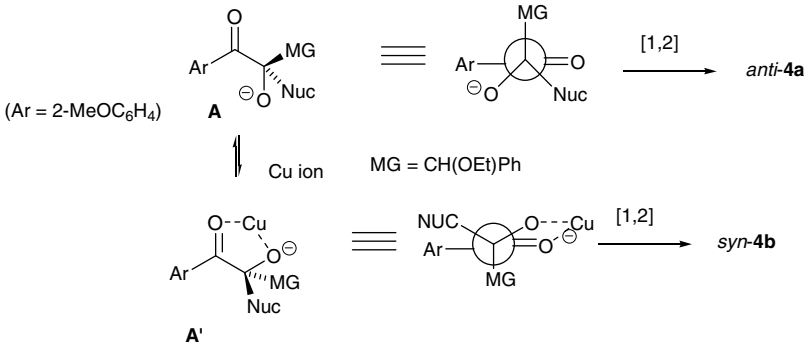
[a] These values were determined by ^{1}H NMR spectroscopy.
[b] A substrate: product ratio of 1:2.3 was obtained as determined by ^{1}H NMR spectroscopy.

with a highest diastereoselectivity of 4.6:1 for the reaction catalysed by only 5 mol % $Cu(OAc)_2$ (entry 5). This phenomenon of increasing diastereoselectivity as the quantity of catalyst is reduced is interesting. This aspect of the BAR/ BER is important considering that for acyclic systems there are no reports of diastereoselective BARs/BERs in the literature (there has been a report of a highly diastereoselective BAR reaction,[15]) despite reports of highly diastereoselective reactions in cyclic systems.[4–6] How can one explain the inverse relationship between copper concentration and reaction diastereoselectivity? It is expected that the most stable conformation for α-diketone **5** (which is obtained from oxidising the hydroxyl group of α-hydroxyketone **3**) is the one shown in Scheme 4 with the *S-trans* conformation, having both carbonyl groups anti-periplanar to avoid dipole–dipole repulsion. The nucleophile (methoxide) will attack C-2 (see discussion above on the regioselectivity) from top and bottom to give the tetrahedral intermediate **6**, which suffers rearrangement to give the α-hydroxy ester product **4**. It would be reasonable to assume that the nucleophile will attack carbonyl-2 according to Cram's rule (or the Felkin-Ahn model; the former model was also invoked by Brady et al.[15] in their study). This would mean that the preferred diastereomeric intermediate **6** (Scheme 4) should have the (2*R*,3*S*; 2*S*,3*R*) configuration. If one considers **6** to exist initially in conformation **A** (Scheme 5) and if Deslongchamps' model,[16] which proposes an orthogonal approach of the migrating group (MG) for maximum orbital overlap is invoked, then the major diastereomer should be (2*S*,3*S*;2*R*,3*R*)-**4** (or *anti*-**4**) which we have previously established to be the major diastereomer in this reaction.[17,18]

At the same time intermediate **A** might coordinate with copper ion to give a chelate (**A′**, Scheme 5) and in this case, an equilibrium would be expected between **A** and



Scheme 4.



Scheme 5.

A′. Using the same argument as before, migration of the MG would give exclusively the *syn*-isomer (Scheme 5). However, as the Cu(II) loading is reduced, the equilibrium should become more in favour of intermediate **A** and thus there would be an increase in the amount of *anti*-diastereomer.

On the basis of literature precedent[15,19] we presume that the chiral migrating group migrates with retention of configuration as it is a nucleophilic 1,2-rearrangement and studies show that this is the case.[19]

In conclusion, we have developed a novel catalytic oxidation/BER process that converts in a regiospecific and stereoselective manner α-hydroxy ketones to tertiary α-hydroxy esters. We have investigated the mechanism of this reaction showing that the group attached to carbonyl-2 exclusively migrates. We are currently investigating intramolecular versions of this reaction and developing this methodology for organic synthesis.

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