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A simple, highly regioselective, one-pot stereoselective synthesis of tertiary α-hydroxyesters: a tandem oxidation/benzilic ester rearrangement

Carolina Sílva Marques, Nuno Moura and Anthony J. Burke*

Departamento de Química and Centro de Química de Évora, Universidade de Évora, Rua Romão Romalho 59, 7000 Évora, Portugal

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Abstract—This letter describes a simple, highly regioselective, stereoselective one-pot tandem oxidation/benzilic ester rearrangement protocol for the conversion of α-hydroxyketones to tertiary α-hydroxyesters.

1. Introduction

Tertiary α-hydroxy carboxylic acids and esters are very important structural units present in a plethora of natural products and medicinal compounds, or in the key intermediates leading to these compounds. For example, the α-hydroxy carboxylic acid unit is present in complex natural products like integerrimine[1] and monocrotaline.[2] The α-hydroxyester unit is present in oxybutynin, a widely used muscarinic receptor antagonist for the treatment of urinary incontinence.[3] Topotecan and irnotecan are two compounds which contain the tertiary α-hydroxyester unit, which are the active ingredients for the treatment of ovarian and colorectal cancer, respectively.[4] It is also present in the glucocorticoid receptor binders reported recently by a team at GlaxoSmithKline.[5]

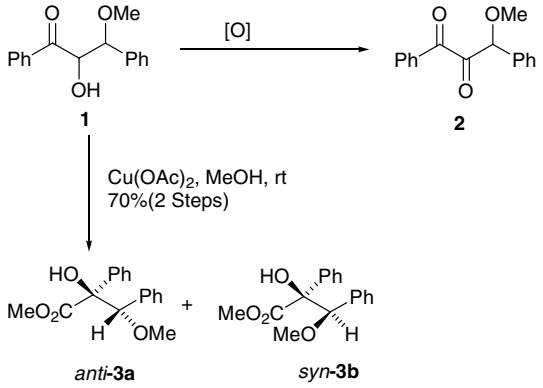
Despite the importance of this functional group, there are quite a limited number of methods available for the direct stereoselective synthesis of the tertiary α-hydroxy carboxylic acid or ester unit. Most methods rely on the addition of organometallic reagents to activated ketones to achieve this objective, like the methods reported by Loupy and Monteux,[6] Fennie et al.[7] and the group of Senanayake[3] where Grignard reagents were added to α-ketoester substrates. Wang et al.[8] obtained α-hydroxy carboxylic acids by the addition of allyltrichlorosilane to α-oxocarboxylic acids. The homo-aldol reaction was also recently exploited for this purpose.[9]

Several years ago, Casiraghi and co-workers used a Lederer–Manasse-type phenoxide addition to a range of chiral pyruvate esters to give *o*-hydroxyatrolactic esters.[10] Dihydroxylation of α,β-unsaturated esters has also been used.[11]

In this letter, we report a simple one-pot tandem oxidation/benzilic ester rearrangement protocol for the synthesis of tertiary α-hydroxyesters from α-hydroxyketones.

2. Discussion

Some time ago, we were interested in using α-diketone **2** (Scheme 1) as a model substrate in order to probe the



Scheme 1.

* Corresponding author. Tel.: +351 266745310; fax: +351 266744971; e-mail: ajb@dquim.uevora.pt

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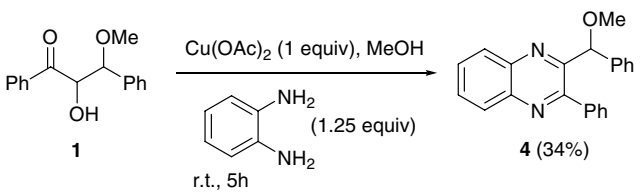
mechanism of a certain benzilic acid rearrangement.[12,13] Our strategy to synthesise **2** was to treat α-hydroxyketone **1** (obtained via acidic methanolysis of chalcone epoxide[12] as a mixture of *anti*- and *syn*-isomers[12]) with a suitable oxidation agent. Many oxidation agents were used without effect, but when $Cu(OAc)_2$ was used in methanol instead of isolating α-diketone **2**, we obtained the tertiary α-hydroxyesters *anti*-**3a** and *syn*-**3b** in a ratio of 1.8:1[14] and with a combined yield of 70%.

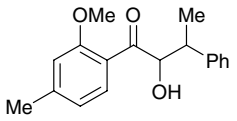
We believe that α-diketone **2** was indeed generated but readily suffered a benzylic ester rearrangement[15] due to the reaction of diketone **2** with methoxide ion.[16] The rearrangement was completely regioselective. To confirm that indeed an α-diketone was generated in this reaction, we conducted the reaction in the same way as before, but added 1,2-diaminobenzene to trap the intermediate α-diketone **2**. This method had been used previously by other workers to establish the generation of α-diketones from α-hydroxybenzofuranones in solution.[17] As expected, quinoxaline **4** was the only product obtained (Scheme 2), thus confirming the generation of α-diketone intermediates in this reaction.

Gratified by these results, we decided to conduct a preliminary study to get an idea of the scope of this reaction and to access the influence of both electronic, stereochemical factors, and the solvent on the reaction efficiency, the regioselectivity and the diastereoselectivity. The following family of α-hydroxyketones **8**–**16** were prepared by selective ring cleavage of epoxy ketones **5**–**7**, which were obtained from the corresponding chalcones via the Weitz–Scheffer epoxidation reaction[18] (Table 1).

Roberts and co-workers[19] recently reported an efficient way of accessing α-hydroxy-β-methylketones **9** and **13** by methylating the corresponding α,β-unsaturated epoxides with the active methylating reagent formed by reacting Me_3Al with water. We applied this procedure to obtain α-hydroxyketones **9** and **13**. A secondary product that could not be removed despite our best efforts contaminated α-hydroxy-β-methylketone **13**. ^1H NMR analysis appeared to identify the secondary compound as a single diastereomer (it was not possible to determine its relative configuration) of α-hydroxy-β-methylketone **17**, presumably obtained via electrophilic methylation of the 1-phenyl ring of either the epoxide starting compound or one of the α-hydroxy-β-methylketone diastereomeric products. For this reason, α-hydroxy-β-methylketone **13** was not used for the tandem oxidation/benzilic ester rearrangement.



Scheme 2.



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To access β-chloro-α-hydroxyketones **10** and **14** we used the procedure of Xu et al.[20] which employed TMSCl as the source of chloride nucleophile.

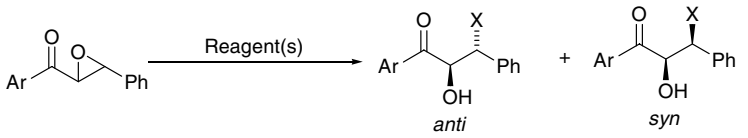
α-Hydroxyketones **8**, **9**, **11**, **12** and **16** were evaluated in a series of room temperature tandem oxidation/benzilic ester rearrangements (Table 2).

Although, the type of substrate we could access limited this preliminary study (which we hope to extend in the near future), we nevertheless obtained some important information relating to this reaction procedure. It was found that in all cases the in situ benzilic ester rearrangement was 100% regioselective, with the nucleophile selectively attacking carbonyl-2. The yields were generally satisfactory for the two steps. Some reasonable preliminary diastereoselectivities were obtained with a maximum of just under 3:1, and it implied that the size of the 1-phenyl ring and the substituent in the 3-position influence the diastereoselectivity.

In the case of β-chloro ketones **10** and **14** no benzilic ester rearrangement occurred. It appears that the presence of a chlorine in the 3-position inhibited the reaction, as only the starting material was obtained. This could be, for the following reasons: (1) the electron withdrawing chlorine prevents 1,2-migration of the CH(Cl)Ph group or (2) the intermediate α-diketone exists predominantly in its enol form (Scheme 3) thus preventing the benzilic ester rearrangement from occurring. β-Acetoxyketone **15** failed to give any tertiary α-hydroxyester product, giving unidentified products instead, perhaps from more favourable competing side reactions. These results appear to indicate that substrates containing electron withdrawing groups in the migrating unit have little propensity to undergo the benzilic ester rearrangement. As an additional study we looked at the effect of temperature on the reaction. The tandem oxidation/benzilic ester rearrangement on α-hydroxyketone **1** using $CuOAc_2$ in methanol at reflux (1.8 h then 4 h at rt) gave the mixture of *anti*-**3a** and *syn*-**3b** with a total isolated yield of 66%. The diastereomeric ratio was not determined.

We feel that this one-pot transformation of appropriate α-hydroxyketones to tertiary α-hydroxyesters fits a number of the requirements listed by Sharpless and co-workers[21] for consideration as a click chemistry process. For instance, it is modular, atom economical (there are no by-products), the reaction conditions are simple, one reagent serves as the solvent and the starting materials are readily available.[22] We are currently investigating this reaction procedure to access other important target compounds and to obtain an asymmetric version.

Table 1.



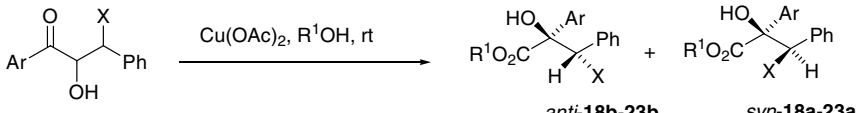
5 Ar = Ph
6 Ar = 2-$MeOC_6H_4$
7 Ar = 2,4-$(MeO)_2C_6H_3$

8 Ar = Ph, X = OEt
9 Ar = Ph, X = Me
10 Ar = Ph, X = Cl
11 Ar = 2-$MeOC_6H_4$, X = OMe
12 Ar = 2-$MeOC_6H_4$, X = OEt
13 Ar = 2-$MeOC_6H_4$, X = Me
14 Ar = 2-$MeOC_6H_4$, X = Cl
15 Ar = 2-$MeOC_6H_4$, X = OAc
16 Ar = 2,4-$(MeO)_2C_6H_3$, X = OMe

Entry	Epoxyketone	Reagent(s)	Product	Reaction time (h)	Yield[a] (%)	*anti*:*syn*[b]
1	**5**	$EtOH/H_2SO_4$	**8**	6	100	2.8:1
2	**5**	Me_3Al/H_2O	**9**	3	92	2:1
3	**5**	TMSCl	**10**	19	70	20:1
4	**6**	$MeOH/H_2SO_4$	**11**	24	91	3.8:1
5	**6**	$EtOH/H_2SO_4$	**12**	42	50	3.5:1
6	**6**	Me_3Al/H_2O	**13**	4	[c]	1.5:1
7	**6**	TMSCl	**14**	19	61	1:20
8	**6**	AcOH	**15**	24	37	3.1:1
9	**7**	$MeOH/H_2SO_4$	**16**	24	90	*syn* only

[a] For both diastereomers.
[b] Determined by ^1H NMR spectroscopy, except for entry 8 where the diastereomeric ratio is based on isolated yields.
[c] Could not be calculated due to the presence of an inseparable side product.

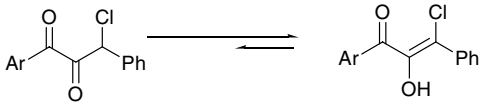
Table 2.



8, 9, 11,12,17

Entry	α-Hydroxyketone	R^1	X	Ar	Product	Reaction time (h)	Yield (2 steps)[a] (%)	*anti*:*syn*[b,c]
1	**8**	Me	OEt	Ph	**18**	72	37	2.8:1
2	**9**	Me	Me	Ph	**19**	45	42	2:1
3	**11**	Me	OMe	2-$MeOC_2H_4$	**20**	44	35	2.9:1
4	**11**	Et	OMe	2-$MeOC_2H_4$	**21**	48	63	2.6:1
5	**12**	Me	OEt	2-$MeOC_2H_4$	**22**	48	49	2.1:1
6	**17**	Me	OMe	2,4-$(MeO)_2C_2H_4$	**23**	94	49	2.9:1

[a] For both diastereomers.
[b] Determined by ^1H NMR spectroscopy.
[c] The assignment of the *anti*-isomer as the major isomer was made on the basis of the literature precedents.[12,13]



Scheme 3.

Acknowledgements

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