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Oxidative rearrangement of 2-alkoxy-3,4-dihydro-2*H*-pyrans: stereocontrolled synthesis of 4,5-cis-disubstituted tetrahydrofuranones including whisky and cognac lactones and crobarbatic acid

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ABSTRACT

Oxidation of 2-alkoxy-3,4-dihydro-2*H*-pyrans **3** with dimethyldioxirane or MTO/urea–H_2O_2 followed by Jones oxidation leads to rearrangement and stereocontrolled formation of 4,5-cis-disubstituted tetrahydrofuranones. The method is applied to the synthesis of the whisky lactone **9**, cognac lactone **10** and crobarbatic acid **17**.

1. Introduction

Tetrahydrofurans (THFs) are key motifs of several classes of biologically important natural product,[1] and methods for their stereocontrolled synthesis are therefore important and actively sought.[2] In 1970, Hall and co-workers reported that oxidation of some simple 2-alkoxy-3,4-dihydro-2*H*-pyrans **3** (R^2–R^4=H) with *m*-CPBA afforded the THFs **4**, presumably via the intermediate epoxide **5** (Scheme 1).[3] Since then, this rearrangement has been exploited in the specific case of spiroketal synthesis, by Ireland[4] and Rizzacasa and McRae.[5] Because a wide range of the starting pyrans **3** may be readily accessed by Lewis-acid promoted hetero-Diels–Alder reaction between an enone and an enol ether, we wished to explore the generality of the oxidative rearrangement process, particularly with regard to diastereoselectivity issues, which had not previously been addressed. Our recent demonstration that diastereoselective aziridination of **3** leads to substituted pyrrolidines with a high level of stereocontrol provided encouragement in this regard.[6] In this paper, we report in full our studies on the oxidative rearrangement of pyrans **3**.

2. Results and discussion

2.1. Synthesis of dihydropyrans 3

We aimed to prepare a wide range of substrates **3** bearing a variety of substitution patterns. Initially, we employed thermal cycloaddition between enones **1** and enol ethers **2** under Yb(FOD) catalysis (Table 1, conditions A).[7] However, these conditions generally required long reaction times (1–10 days). Therefore, we investigated microwave conditions (conditions B), which allowed completion in much shorter times (2–3 h). Where applicable, the cycloadditions afforded predominantly one diastereomer. Literature precedent[7] suggests that the major diastereomer is the *endo*-cycloadduct, with the *C*2-alkoxy group and the *C*4-substituent R^3 in a cis-relationship. Analysis of ^{1}H NMR coupling constants for the major product supported by molecular mechanics analysis (MMFF, Spartan) suggested that H2 is pseudoaxial (J_{H2-H3} 7.0–9.5 Hz) and thus both the *C*2-alkoxy substituent and the *C*4-substituent R^3 are likely to be pseudoequatorial. On standing in $CDCl_3$, the major *endo*-diastereomer underwent epimerisation to the minor *exo*-isomer, having a pseudoaxial alkoxy group (J_{H2-H3} 2.5–3.0 Hz), preferred due to the anomeric effect.

2.2. Oxidative rearrangement of 6-substituted pyrans

With a convenient synthesis of substrates **3** in hand, we were now in a position to test their epoxidation/rearrangement. Initially, we employed the least substituted substrate **3a** to screen several common epoxidation reagents (Table 2). Reaction of **3a** with commercial *m*-CPBA in CH_2Cl_2 (entry 1) afforded only a low yield (14%) of the desired THF **4a**, along with the lactol **6** (ca. 10%), presumably arising from hydrolysis of **4a**. Concerns that the low yield of **4a** may be partly due to its volatility led us also to test the ^{n}Bu-substrate **3b** under these conditions (entry 2). A higher yield of **4** (39%) was indeed obtained, and smaller quantities of hydrolysis product **6**. Next, we tested isolated solutions of dimethyldioxirane (DMDO)[8] (entries 3 and 4). Surprisingly, the major reaction product in this case was the lactol **6**, even when the acetone solutions of DMDO solutions were dried over K_2CO_3 prior to use. The combined product yield (yield of **4**+yield of **6**) was, however, better with DMDO than with *m*-CPBA. Potential difficulties in preparing DMDO solutions on large scale prompted us to

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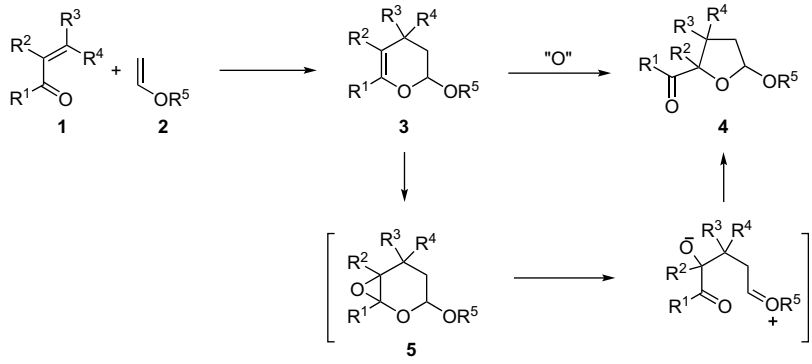
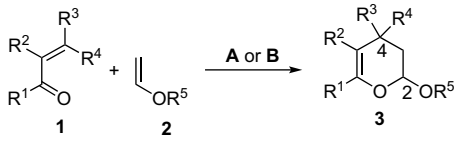


Scheme 1.

attempt in situ formation of DMDO[9] from acetone and Oxone (entries 5 and 6). The reaction with the less volatile substrate **3b** afforded a highly promising combined product yield (76%, entry 6), but the longer reaction times meant that we preferred to use isolated DMDO solutions in subsequent investigations. An attempt at using the more reactive trifluoroacetone/Oxone system[10] with **3b** did not provide any of the desired product.

In order to simplify product analysis and purification, and also to facilitate eventual stereochemical analysis, we wished to convert the mixture of lactol ethers **4** and lactols **6** into a common product.

Table 1
Enone/enol ether hetero Diels–Alder reaction



Entry	R^1	R^2	R^3	R^4	**1**	R^5	**2**	**3**	Yield[i]	dr[j]
1[a]	Me	H	H	H	**1a**	Et	**2a**[c]	**3a**	70	N/A
2[a]	Me	H	H	H	**1a**	^{n}Bu	**2b**[d]	**3b**	55	N/A
3[a]	Me	H	Me	H	**1b**	^{n}Bu	**2b**[d]	**3c**	40	6:1
4[a]	Me	H	^{i}Pr	H	**1c**	^{n}Bu	**2b**[d]	**3d**	75	6:1
5[a]	Me	H	Me	Me	**1d**	^{n}Bu	**2b**[e]	**3e**	54	N/A
6[a]	Me	H	Ph	H	**1e**	Et	**2a**[e]	**3f**	50	≥99:1
7[a]	Me	H	CH_2OBn	H	**1f**	Et	**2a**[f]	**3g**	67	≥99:1
8[a]	Me	H	$(CH_2)_4CH{=}CHEt$	H	**1g**	Et	**2a**[f]	**3h**	56	4:1
9[a]	H	H	Ph	H	**1h**	Et	**2a**[g]	**3i**	100	≥99:1
10[b]	H	H	Ph	H	**1h**	Et	**2a**[h]	**3i**	89	≥99:1
11[a]	H	H	Me	H	**1i**	Et	**2a**[e]	**3j**	88	≥99:1
12[b]	H	H	Me	H	**1i**	Et	**2a**[e]	**3j**	66	≥99:1
13[a]	H	H	CH_2OBn	H	**1j**	Et	**2a**[e]	**3k**	99	≥99:1
14[b]	H	H	^{i}Pr	H	**1k**	Et	**2a**[e]	**3l**	58	≥99:1
15[b]	H	H	*p*-MeO C_6H_4	H	**1l**	Et	**2a**[e]	**3m**	98	≥99:1
16[a]	H	H	Et	H	**1m**	Et	**2a**[e]	**3n**	98	≥99:1
17[a]	H	Me	H	H	**1n**	Et	**2a**[e]	**3o**	91	N/A
18[a]	H	Me	Me	H	**1o**	Et	**2a**[e]	**3p**	90	≥99:1
19[a]	H	Me	Et	H	**1p**	Et	**2a**[e]	**3q**	93	≥99:1
20[a]	H	Me	Ph	H	**1q**	Et	**2a**[e]	**3r**	85	≥99:1
21[b]	H	Me	Furyl	H	**1r**	Et	**2a**[e]	**3s**	13	≥99:1
22[b]	H	Me	OEt	H	**1s**	Et	**2a**[e]	**3t**	26	≥99:1
23[b]	H	^{n}Bu	H	H	**1t**	Et	**2a**[e]	**3u**	85	N/A
24[b]	H	Ph	Me	H	**1u**	Et	**2a**[e]	**3v**	91	3:1
25[b]	Ph	H	H	H	**1v**	Et	**2a**[e]	**3w**	48	N/A
26[b]	Ph	H	Me	Me	**1w**	Et	**2a**[e]	**3x**	41	N/A
27[b]	Ph	H	Et	Et	**1x**	Et	**2a**[e]	**3y**	12	N/A
28[b]	Ph	H	CyHex		**1y**	Et	**2a**[e]	**3z**	30	N/A
29[b]	*p*-MeO C_6H_4	H	Me	Me	**1z**	Et	**2a**[e]	**3aa**	27	N/A
30[b]	*p*-Me C_6H_4	H	Me	Me	**1aa**	Et	**2a**[e]	**3ab**	40	N/A
31[b]	*p*-Cl C_6H_4	H	Me	Me	**1ab**	Et	**2a**[e]	**3ac**	44	N/A
32[b]	*p*-NO_2 C_6H_4	H	Me	Me	**1ac**	Et	**2a**[e]	**3ad**	58	N/A
33[b]	2-Naphthyl	H	Me	Me	**1ad**	Et	**2a**[e]	**3ae**	41	N/A

[a] Conditions A: pressure tube, 45–100 °C, YbFOD catalyst (2–5 mol %), 1–10 days.
[b] Conditions B: microwave, 55–80 °C, YbFOD catalyst (5 mol %), 2–6 h.
[c] 7 equiv of **2** to **1**.
[d] 2 equiv of **2** to **1**.
[e] 5 equiv of **2** to **1**.
[f] 10 equiv of **2** to **1**.
[g] 12 equiv of **2** to **1**.
[h] 6 equiv of **2** to **1**.
[i] Combined yield of diastereoisomers (%).
[j] The ratio of *endo* to *exo* determined by ^{1}H NMR.