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Electrochemical oxidative cyclisation of ω-hydroxy-tetrahydropyrans to spiroketals†

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Abstract

Substituted spiroketals can be readily accessed by the electrochemical oxidative cyclisation of ω-hydroxy-tetrahydropyrans.

Keywords: electrochemistry; cyclisation; spiro compounds; oxidation.

The spiroketal motif **1** is ubiquitously present in numerous biologically active natural products encompassing insect pheromones, marine toxins and microbial metabolites. The widespread occurrence of spiroketals coupled with their key role as pharmacophores, has stimulated the development of a range of elegant methodologies for their efficient and stereocontrolled assembly.[1] Our interest in the total synthesis of spiroketal-containing natural products led us to investigate various procedures for the construction of this important subunit.[2] In this context, the oxidative cyclisation of ω-hydroxy-tetrahydropyrans (Fig. 1) appeared particularly attractive for our purpose.

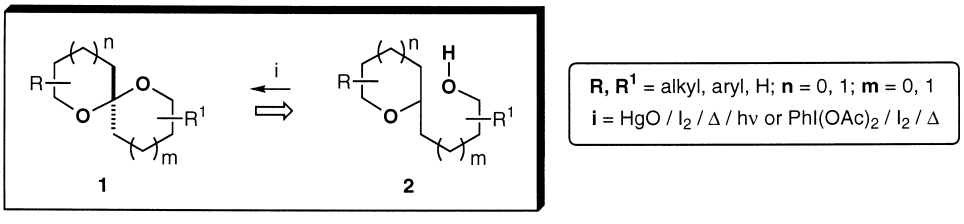

Figure 1.

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† Dedicated with deep respect to Professor Sigeru Torii.

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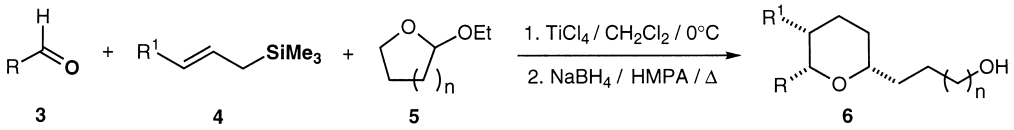
Unfortunately, the conditions required to perform the transformation of **2** into **1** typically employ large amounts of either expensive, hazardous or toxic reagents.[3] In order to raise this limitation and to provide a more environmentally friendly protocol for this useful reaction, we decided to investigate the electrochemical oxidative cyclisation of substrates such as **2**. The requisite ω-hydroxy-tetrahydropyrans **2** were readily prepared according to our recently reported four-component condensation methodology.[4] This efficient procedure, which is based upon a modification of a protocol first introduced by Taddei and Ricci,[5] involves the condensation of an aldehyde **3**, an allylsilane **4** and a cyclic acetal **5** in the presence of $TiCl_4$ (Fig. 2). The intermediate chlorotetrahydropyrans are reductively dechlorinated affording the desired ω-hydroxy-tetrahydropyrans **6**.



3 **4** **5** **6**

Entry	Product	R	R^1	n	Yield[(a)]
1	**6a**	C_6H_{13}	H	1	62%
2	**6b**	C_6H_{13}	H	2	59%
3	**6c**	$(C_2H_5)_2CH$	H	1	65%
4	**6d**	$(C_2H_5)_2CH$	H	2	60%
5	**6e**	$(C_2H_5)_2CH$	Me	2	58%

[(a)] Overall yield of pure, isolated product for the two step protocol.

Figure 2.

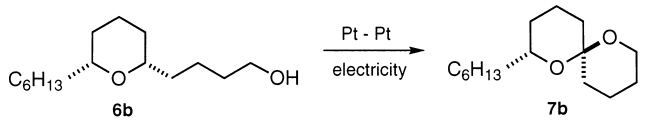
With ready access to a variety of starting substrates, we next turned our attention to the crucial electrochemical oxidative cyclisation step. Some pertinent conditions are displayed in Table 1.

Preliminary investigations using substrate **6b** and NaI as the additive,[6,7] with the hope of generating in-situ the corresponding hypoiodide, failed to give the cyclised product **7b** (Table 1, Entries 1 and 2). In both cases, the starting material **6b** was recovered unaffected, regardless of the presence or absence of an added electrolyte. A similar lack of reactivity was also observed when the electrocyclisation was attempted under the conditions of Finkelstein[8] (Table 1, Entry 3).

The failure to produce any spiroketal under neutral conditions prompted us to investigate the electrochemical cyclisation of **6b** under basic conditions. The enhanced facility of generating an alkoxy radical by abstraction of an electron from the corresponding alkoxide ion, as compared to the neutral alcohol function, has been reported in the literature.[9] We were gratified to find that electrolysis of alcohol **6b**, in a mixture of MeCN and ^{t}BuOH containing 0.5 equiv. KOBu^t, afforded the desired spiroketal **7b**, although in a modest 13% yield. Repeating the reaction in MeOH containing NaOMe led to an analogous outcome (Table 1, Entries 4 and 5). Numerous by-products were also formed in these electrochemical oxidations, originating from self condensation of MeCN and Hoffmann degradation of the quaternary ammonium salt.[10]

Replacing Bu_4NBF_4 by Me_4NBF_4, an electrolyte that does not suffer Hoffmann elimination, resulted in a significant increase in the yield of spiroketal **7b** (Table 1, Entry 6). A similar result

Table 1
Optimising the conditions for the electrochemical spiroketalisation of **6b**



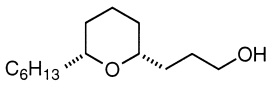
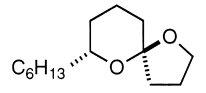
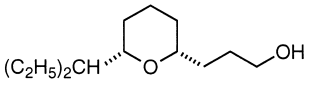
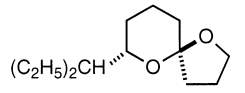
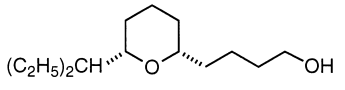
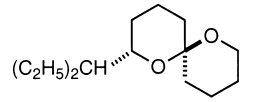
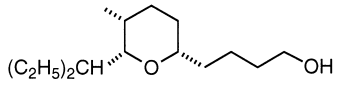
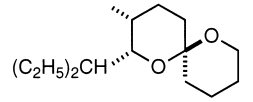
6b **7b**

Entry	Solvent	Electrolyte	Additives	Yield[(a)]
1	MeOH	-	NaI	-
2	MeOH	Et_4NBF_4	NaI	-
3	DMF	Me_4NBF_4	-	5 %
4	MeCN / ^{t}BuOH	Bu_4NBF_4	^{t}BuOK (0.5 eq)	13 %
5	MeOH	Bu_4NBF_4	NaOMe (1 eq)	15 %
6	MeOH	Me_4NBF_4	NaOMe (1 eq)	30 %
7	MeOH	$LiBF_4$	NaOMe (2 eq)	25 %
8	**EtOH**	**$LiBF_4$**	**NaOEt (2 eq)**	**61 %**

[(a)] All yields refer to pure, isolated products. The reactions were performed under argon, in an undivided cell, at 20°C, with a constant current of 0.1 A.

was obtained when the ammonium salt was substituted by $LiBF_4$ (Table 1, Entry 7). Finally, the use of $LiBF_4$ and NaOEt in anhydrous ethanol afforded the desired spiroketal **7b** in 61% isolated yield (Table 1, Entry 8). These conditions were then applied to the electrochemical oxidative cyclisation of a representative range of ω-hydroxy-tetrahydropyrans **6**. The results are collected in Table 2.

Table 2
Electrochemical oxidative spirocyclisations

Entry	Substrate	Product	Yield[(a)]
1			54%
2			51%
3			57%
4			60%

[(a)] All yields refer to pure, isolated products

As shown in Table 2, both [4,5] and [5,5] spiroketals can be obtained in good yields using this electroorganic technique. The methodology is competitive with previously reported protocols.[11] Furthermore, the reaction conditions are much milder and the isolation of the final product is greatly simplified.

A plausible mechanism for this oxidative cyclisation probably involves an initial equilibrium between the starting alcohol **6** and the corresponding alkoxide **8** (Fig. 3). Loss of an electron from **8** then generates an alkoxy radical **9** which undergoes an intramolecular hydrogen abstraction from C_6 of the tetrahydropyran nucleus, generating the stabilised C-centred radical **10**. Further oxidation of this radical then leads to the *oxo*-carbenium ion **11** which is intercepted intramolecularly by the pendant hydroxyl function affording, after deprotonation, the final spiroketal subunit **7**.

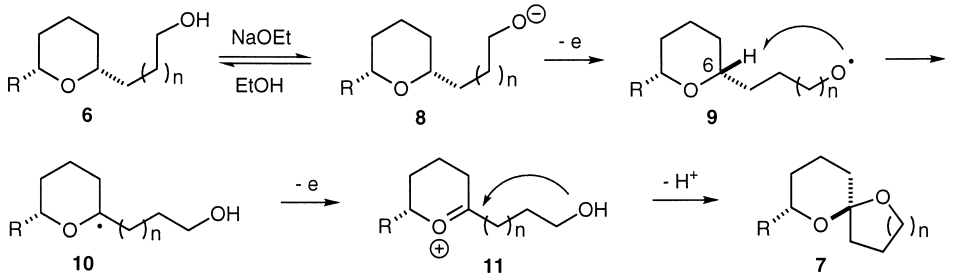


Figure 3.

In summary, we have shown that ω-hydroxy-tetrahydropyrans **6** can be converted in good yields into [4,5] and [5,5] spiroketals when subjected to electrochemical oxidation in the presence of a suitable base and electrolyte. Our protocol possesses several advantages over preexisting methodologies, one of the most noteworthy being the lack of toxic or hazardous stoichiometric reagents, such as mercury salts.[3] Further studies are directed at improving the yields and broadening the scope of this useful spiroketalisation protocol as well as delineating the intimate mechanism of this electrochemical transformation.

Acknowledgements

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11. **Typical experimental procedure**: NaH (30 mg, 2 equiv., 0.5 mmol) is added to anhydrous ethanol (10 mL), placed in an undivided electrolysis cell, fitted with two 1 cm^2 Pt electrodes, and maintained under argon. After 10 min, the colourless solution of NaOEt is cooled to 0°C (ice bath) and 21 mg of $LiBF_4$ (1 equiv., 0.25 mmol) are added followed by substrate **6b** (60 mg, 1 equiv., 0.25 mmol) dissolved in 1 mL of EtOH. Electricity (0.09 A, 9 volts) is then passed through the reaction medium over 3 h (in some cases, the voltage has to be adjusted to keep a constant 0.09 A throughout the reaction). After 3 h, water (10 mL) and petroleum ether (10 mL) are then added. The organic layer is separated and the aqueous phase is extracted with another 10 mL portion of petroleum ether. The organic layers are pooled, dried over $MgSO_4$ and the solvent is removed in vacuo, affording crude **7b** as a yellow oil. Purification by silica gel column chromatography (CH_2Cl_2) gave pure **7b** (37 mg, 61%) as a colourless oil. ^1H NMR ($CDCl_3$; 200 MHz) δ: 3.6 (m, 3H), 1.8 (m, 2H), 1.6–1.2 (m, 20H), 0.9 (t, $J = 7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.09, 18.63, 18.89, 22.65, 25.49, 25.86, 29.48, 31.26, 31.90, 35.48, 35.97, 36.51, 60.32, 69.11, 97.43. Capillary GC (polymethylsiloxane, 1% vinyl, 2% phenyl; WCOT, Macherey-Nagel, L = 30 m, 0.25 mm diameter, 25 μ film; FID), injection temperature: 100°C, 10°C per min gradient; retention times: **6b** 14.01 min; **7b** 11.87 min.