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Highly selective SmI_2–H_2O-promoted radical cyclisation of five-membered lactones

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ABSTRACT

Radicals formed by SmI_2–H_2O-mediated electron transfer to the carbonyl group of unsaturated five-membered lactones undergo diastereoselective cyclisation to give cyclohexane-1,4-diols. The use of HMPA as an additive with SmI_2–H_2O gave improved conversion and diastereoselectivity in the cyclisations.

1. Introduction

Oxygenated cyclohexanes are ubiquitous substructures among complex terpenes with a high biological profile and new stereoselective methods for their facile formation are always in demand (Fig. 1A).[1–6] Samarium diiodide (Kagan's reagent, SmI_2)[7] has a long track record in the selective formation of carbon–carbon bonds.[8] We have recently expanded the already large repertoire of SmI_2 by developing new substrate activation modes involving electron transfer (ET) to carboxylic acid derivatives using SmI_2–H_2O under mild conditions.[9] This discovery has led to our development of novel functional group transformations[10–17] and highly selective radical cyclisation processes involving carbon–carbon bond formation.[10b,11a,17–20]

The reactivity of the radical anion formed during the SmI_2–H_2O-promoted reduction of carboxylic acid derivatives is a key factor in these reactions.[9] For example, in the reduction of lactones using SmI_2–H_2O, radical intermediates are stabilised by hyperconjugation with the neighbouring oxygen atoms and also by H_2O.[10a,10b,10d] We recently demonstrated that the first electron transfer to the lactone carbonyl is reversible for lactones of various ring sizes[10d,16] and this reversibility can limit the ability to do productive chemistry. For example, six-membered lactones can be reduced to diols using SmI_2–H_2O as the intermediate radical anions

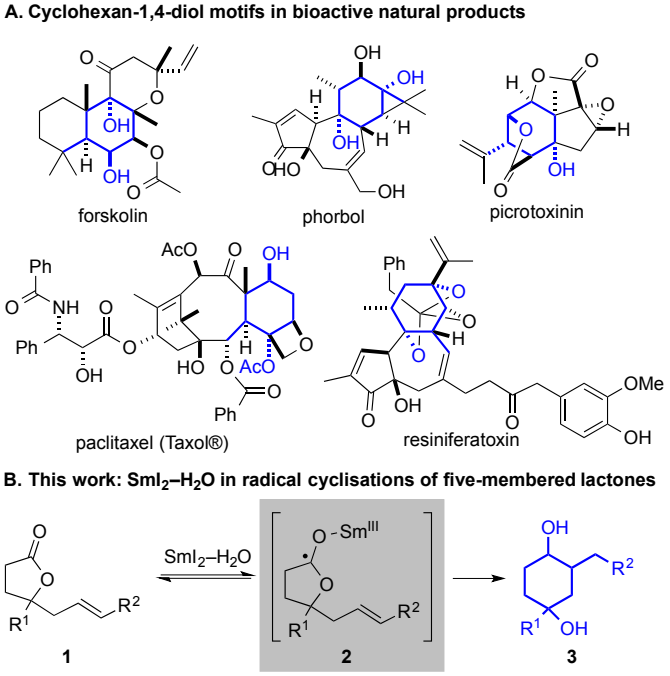

Fig. 1. A. Selected natural products containing cyclohexane-1,4-diol motifs. B. Radical cyclisation of five-membered lactones using SmI_2–H_2O.

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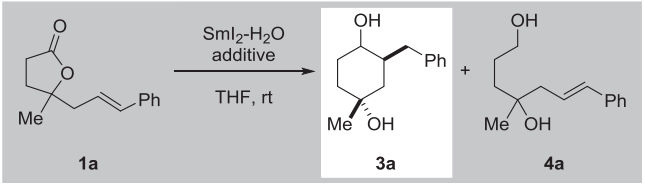
are quickly reduced.[10a,10b] The analogous reduction of five-membered lactones to diols, however, cannot be achieved with SmI_2–H_2O as the corresponding radical anions undergo back ET to Sm(III).[10a,10b,10d] Nevertheless, reductive transformations of five-membered lactones **1** using SmI_2–H_2O may be possible if the radical anion **2** could be efficiently trapped by an appropriately placed radical acceptor prior to back ET to Sm(III). Importantly, trapping radical anions **2** would result in carbon–carbon bond formation and deliver cyclohexan-1,4-diols **3** after in situ reduction of a cyclohexanone intermediate (Fig. 1B). Here we describe the first cyclisations of simple five-membered lactones triggered by single ET to the lactone carbonyl.

2. Optimisation of the cyclisation

The feasibility of the radical cyclisation was assessed using the five-membered lactone **1a** (Table 1). Pleasingly, cyclisation product **3a** was formed cleanly using SmI_2–H_2O, with only traces of acyclic diol byproduct **4a** formed. Increasing the amount of H_2O from 800 to 1600 equiv (100 and 200 equiv wrt SmI_2, respectively; entries 1 and 2) did not affect the conversion or the diastereoselectivity of the reaction. Higher amounts of H_2O, however, had an increasingly detrimental effect on both conversion and diastereoselectivity (entries 3 and 4), and a larger amount of reduction product **4a** was also observed. The recovery of starting material after treatment with excess SmI_2 highlights the low reactivity of the radical anion intermediate (cf. **2**) and the reversibility of the ET step. Long reaction times and variable conversion using SmI_2–H_2O prompted us to screen different additives. First, we observed that the addition of NEt_3[21] to SmI_2–H_2O had a beneficial effect, showing full conversion and higher yields of **3a** (entries 5–8), however, significantly lower diastereoselectivity was observed. The use of low amounts of NEt_3 additive resulted in low conversion and the original diastereoselectivity was reestablished (entries 9 and 10). We have previously shown that SmI_2–H_2O and NEt_3 can reduce all lactones to diols.[10c]

Table 1
Optimisation of the radical cyclisation of five-membered lactone **1a**



1a **3a** **4a**

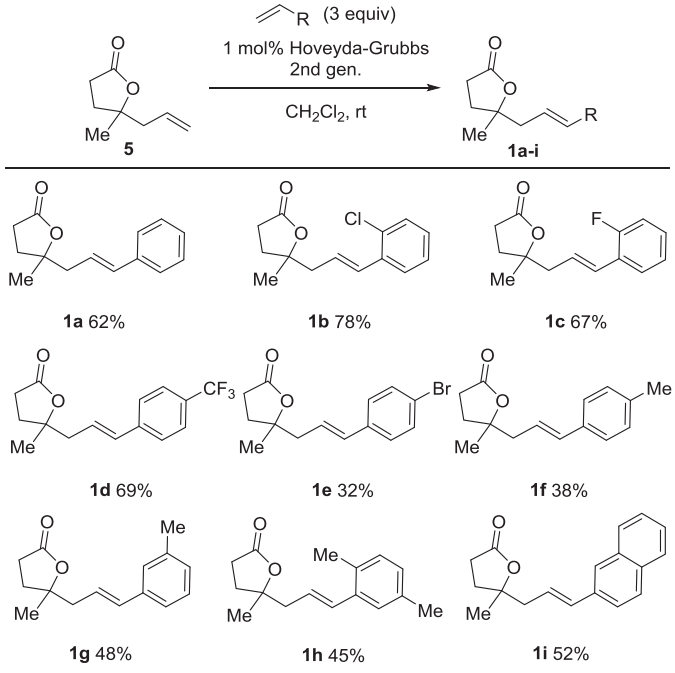
Entry	H_2O (equiv)	Additive (equiv)	**1a** (%)[a]	Conversion (%)[a]	
				3a (dr)[a]	**4a**
1	800[b]	—	34	65 (88:12)	1
2	1600[b]	—	33	63 (88:12)	4
3	2400	—	33	57 (81:19)	9
4	3200	—	58	33 (74:16)	9
5	800	NEt_3 (60)	—	97 (74:16)	3
6	800	NEt_3 (30)	—	86 (71:29)	14
7	800	NEt_3 (15)	—	94 (72:28)	6
8	800	NEt_3 (8)	—	86 (77:23)	14
9	800	NEt_3 (4)	24	69 (79:21)	7
10	800	NEt_3 (1)	44	53 (86:14)	3
11	800	HMPA (8)	16	81 (88:12)	3
12	800	HMPA (16)	5	93 (87:13)	2
13	800[b]	HMPA (32)	36	64 (90:10)	—
14	800[b]	HMPA (64)	21	79 (92:8)	—

Conditions: **1a** (1 equiv), SmI_2 (8 equiv), H_2O (see table), additive (see table), THF, rt.
[a] Conversions and diastereoisomeric ratios determined by NMR analysis.
[b] An average of multiple runs.

Finally, we investigated the effect of HMPA as an additive[22] with SmI_2–H_2O. Pleasingly, the addition of HMPA had a positive effect on the conversion of **1a** into **3a** (entries 11–14) and greater diastereoselectivity was observed at higher concentrations of HMPA.

3. Scope of the cyclisation

With various effective cyclisation conditions in hand, we next synthesised a range of lactone substrates to assess the generality of the process: easily accessible lactone **5**[23] underwent cross-metathesis[24] with various styrenes to give lactones **1a**–**i** in moderate to good isolated yield (Scheme 1).



Scheme 1. Synthesis of lactone cyclisation substrates **1a**–**1i**.

Substrates **1a**–**i** underwent cyclisation upon treatment with SmI_2–H_2O and SmI_2–H_2O–HMPA (Scheme 2). In most cases, oxidation of the cyclisation products **3** using the Dess–Martin periodinane (DMP) was used to simplify isomeric mixtures and clarify the diastereoselectivity of the cyclisation event. This transformation also offers a versatile platform to access other compounds of significant synthetic potential.[25] X-ray crystallographic analysis of **6a** and **6b** confirmed the relative configuration of the major diastereoisomers arising from the cyclisation (Fig. 2).[26] Conversion was found to be inconsistent when SmI_2–H_2O was used possibly due to variability in the decay of Sm(II) over the extended reaction times. When HMPA was used as an additive, higher conversion and higher diastereoselectivity were observed. Substitution in all positions of the aryl substituent on the alkene was tolerated and products were obtained in moderate to good isolated yields. Interestingly, lactones **1b** and **1c** containing a halide substituent in the 2-position of the aryl group on the alkene, gave the corresponding cyclisation products **6b** and **6c**, respectively, with higher diastereocontrol than that observed for other substrates. Furthermore, the use of HMPA as an additive increased the selectivity of the cyclisations of **1b** and **1c**, and **6b** and **6c** were obtained in ≥95:5 dr and 93:7 dr, respectively.