Base-induced cyclization of 1-benzyloxy-2,2,4,4-tetramethylpentan-3-ones: intramolecular nucleophilic addition of an anion of a benzyl ether to the carbonyl moiety without the Wittig rearrangement or protophilic decomposition

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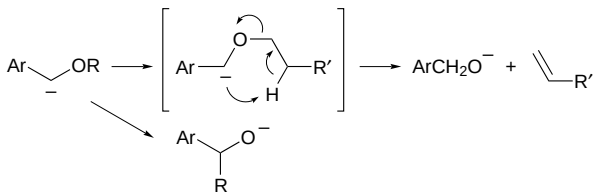
Alkyl benzyl ethers bearing a carbonyl moiety in the alkyl chain (1) cyclize effectively, without the Wittig rearrangement or protophilic decomposition, to give hydroxytetrahydrofurans (*trans*-2) on treatment with Bu^{t}OK in DMSO at room temperature, whereas LDA–THF induces the cyclization of 1 to afford predominantly the stereoisomer *cis*-2.

The α-carbanion of an alkyl benzyl ether is unstable and undergoes protophilic cleavage (elimination)[1,2] or Wittig rearrangement[3–5] even at low temperature (Scheme 1), so that little is known of its nucleophilic addition or substitution reactions, although extensive studies have been made on the rearrangement and the decomposition.[6] We report here that (i) the α-carbanion of an alkyl benzyl ether is able to add effectively to a carbonyl moiety in the alkyl chain *via* intramolecular nucleophilic addition without Wittig rearrangement or protophilic decomposition, and (ii) the addition is sterically controlled by the base–solvent system used.

When benzyl ether **1a** (1.1 g, 4.0 mmol) was treated with Bu^{t}OK (8.0 mmol) in DMSO (12 ml) under N_2 at room temperature for 4 h, **1a** was exclusively transformed into tetrahydrofuran *trans*-**2a** (91%), which was isolated as a colourless oil in 88% yield after chromatographic purification (SiO_2) (Table 1, entry 1). The structure of *trans*-**2a** was determined by ^{1}H NMR, NOESY, IR and mass spectral analysis.† A combination of base and solvent, *e.g.* Bu^{t}OK–THF or MeONa–DMSO, was ineffective for the cyclization of **1a**. On the other hand, after treatment of **1a** with LDA–THF at room temperature for 2 h, the cyclization took place smoothly to afford a stereoisomer *cis*-**2a** as colourless crystals (mp 83.0–83.5 °C) together with a small amount of *trans*-**2a** (*cis* : *trans* = 82 : 18) (94%) (entry 2). When the cyclization was carried out at 0 °C, the stereoselectivity was somewhat improved (*cis* : *trans* = 91 : 9) (entry 3). The reaction of **1a** with LDA–THF proceeded sluggishly at −78 °C. The other benzyl ethers **1b**–**d** also underwent base-induced cyclization to afford the corresponding tetrahydrofurans **2b**–**d** with similar stereoselectivities, as shown in Table 1. It is noteworthy that even benzyl ether **1c** bearing an electron-donating substituent at the *para*-position underwent cyclization in LDA–THF, even though Bu^{t}OK–DMSO was ineffective (entries 6 and 7).

The present results showed that (i) an alkyl benzyl ether is probably stable enough to undergo nucleophilic reaction



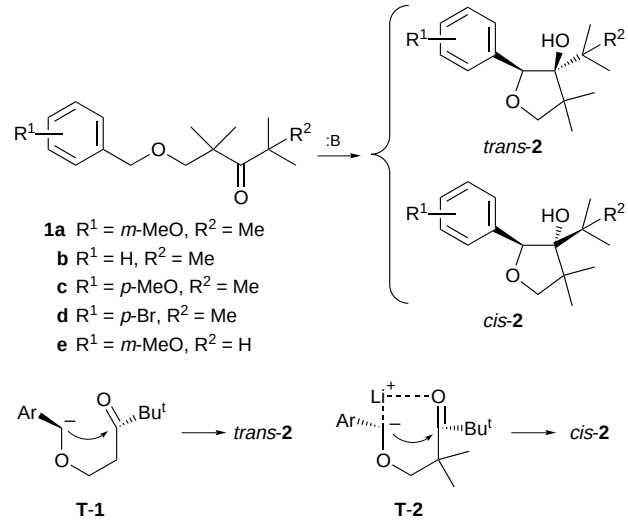
Scheme 1

Table 1 Base-induced cyclization of alkyl benzyl ethers **1**

Entry		System[a]	*t*/h[b]	Conversion (%)[c]	Ratio *trans* : *cis*[d]
1	**1a**	A	4	91	**2a** 100 : 0
2	**1a**	B	2	94	**2a** 80 : 82
3	**1a**	B	2[e]	95	**2a** 9 : 91
4	**1b**	A	4	92	**2b** 100 : 0
5	**1b**	B	2	99	**2b** 9 : 91
6	**1c**	A	4	0	— —
7	**1c**	B	5[f]	86	**2c** 12 : 88
8	**1d**	A	4	99	**2d** 100 : 0
9	**1d**	B	2	96	**2d** 10 : 90
10	**1e**	A	4	72	**2e** 93 : 7
11	**1e**	B	5[f]	63[g]	**2e** 13 : 87

[a] A: **1** (4.0 mmol), Bu^{t}OK (8.0 mmol), DMSO (12 ml). B: **1** (4.0 mmol), LDA (8.0 mmol), THF (12 ml). [b] Carried out at room temp. unless stated otherwise. [c] No product other than **2** was observed, unless stated otherwide. [d] Determined *via* ^{1}H NMR analysis of the crude product. [e] Reaction performed at 0 °C. [f] Reaction performed at −78 °C for 2 h and then at room temp. for 3 h. [g] *trans*-**2e** (5.5%), *cis*-**2e** (31%) and **1e** (37%) recovered after chromatography.

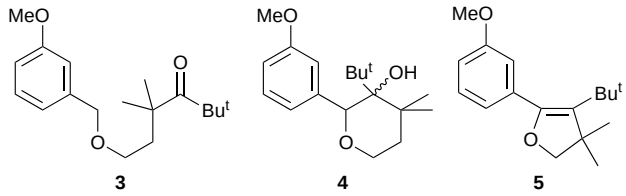
without Wittig rearrangement or decomposition, so long as an electrophile such as a carbonyl moiety exists in a favourable situation, and (ii) the stereoselectivity of cyclization is tightly controlled by the base–solvent system used. The stereoselectivity can probably be rationalized as follows: for the Bu^{t}OK–DMSO system, a naked anion of **1** attacks the carbonyl *via* transition state **T-1**, in which interaction between the aryl and *tert*-butyl groups is minimized, thus giving the sterically less congested isomer *trans*-**2** (Scheme 2). On the other hand, in the



Scheme 2

LDA–THF system a lithium ion might coordinate the carbonyl oxygen and the benzyl α-carbanion in transition state **T-2** to afford *cis*-**2** predominantly, even though the repulsive interaction between the aryl and *tert*-butyl moieties is thermodynamically unfavourable. This rationalization is consistent with the effect of temperature on the stereoselectivity in the cyclization of **1a** using LDA–THF. It is noteworthy that 18-crown-6 promoted the *trans*-selective cyclization of **1a** with Bu^{t}OK in THF to give *trans*-**2a** exclusively (room temp. for 4.5 h; 87%).

Since the substrate **1** lacks a β-hydrogen on the alkyl chain, it is not susceptible to protophilic decomposition to form a terminal alkene (Scheme 1), but it should undergo [1,2]-Wittig rearrangement. Thus, we examined the reaction of benzyl ether **3** as a representative ether bearing β-hydrogens on the alkyl chain. Treatment of **3** with LDA in THF (−78 °C to room



3 **4** **5**

temp.) gave the expected cyclization product **4** in high yield,‡ while the use of Bu^{t}OK–DMSO induced almost no reaction. Thus, intramolecular nucleophilic addition of the α-carbanion of an alkyl benzyl ether to the carbonyl of the alkyl site takes place effectively even if it bears β-hydrogens. In addition, we should note that benzyl ether **1e** bearing an isobutyryl moiety also gave the corresponding cyclization product **2e** on treatment with a base even though **1e** possesses an acidic proton adjacent to the carbonyl moiety (entries 10 and 11).

Both isomeric hydroxytetrahydrofurans *trans*- and *cis*-**2a** were easily dehydrated to give dihydrofuran **5**, which is a key intermediate for the synthesis of a dioxetane used as a highly efficient chemiluminescent substrate[7]§ in high yield upon treatment with $SOCl_2$ and pyridine at room temperature. The other furans **2** obtained here were similarly dehydrated to give the corresponding dihydrofurans.

The present results show that the α-carbanion of an alkyl benzyl ether such as **1** or **3** undergoes nucleophilic addition to a carbonyl moiety existing in the same molecule without Wittig rearrangement or protophilic decomposition. Furthermore, the present cyclization should form a facile entry to sterically crowded cyclic enol ethers.

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Footnotes and References

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† All products obtained here gave satisfactory NMR, IR and mass spectral data.

‡ A single isomer, with stereochemistry tentatively assigned as *cis*-**4** was isolated in 90% yield.

§ Previously, the dihydrofuran **5** had been synthesized by the McMurry reaction of 3-oxo-2,2,4,4-tetramethylpentyl 3-methoxybenzoate using Ti^0 (ref. 7). However, this method is expensive and not suitable for large-scale synthesis.

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