

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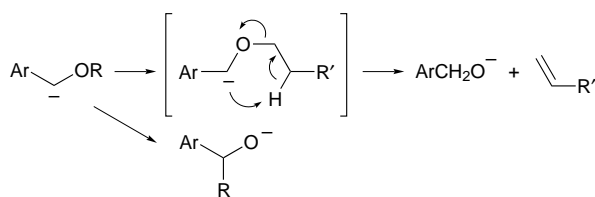
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Alkyl benzyl ethers bearing a carbonyl moiety in the alkyl chain (**1**) cyclize effectively, without the Wittig rearrangement or protophilic decomposition, to give hydroxytetrahydrofurans (*trans*-**2**) on treatment with Bu<sup>t</sup>OK in DMSO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

The  $\alpha$ -carbanion of an alkyl benzyl ether is unstable and undergoes protophilic cleavage (elimination)<sup>1,2</sup> or Wittig rearrangement<sup>3–5</sup> 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.<sup>6</sup> We report here that (i) the  $\alpha$ -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<sup>t</sup>OK (8.0 mmol) in DMSO (12 ml) under N<sub>2</sub> 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<sub>2</sub>) (Table 1, entry 1). The structure of *trans*-**2a** was determined by <sup>1</sup>H NMR, NOESY, IR and mass spectral analysis.† A combination of base and solvent, *e.g.* Bu<sup>t</sup>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<sup>t</sup>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



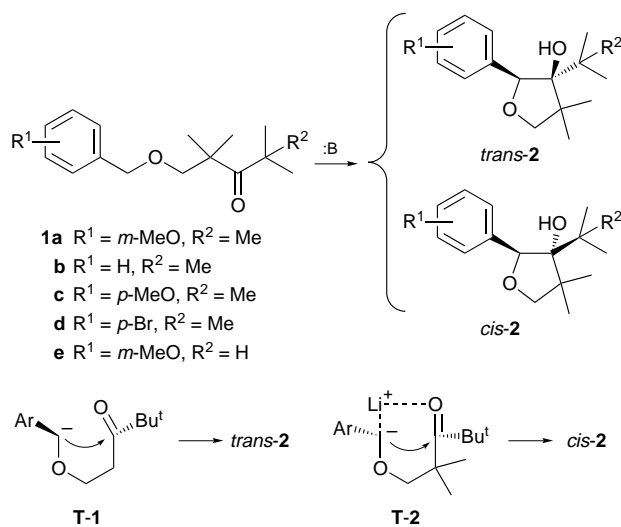
Scheme 1

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

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

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

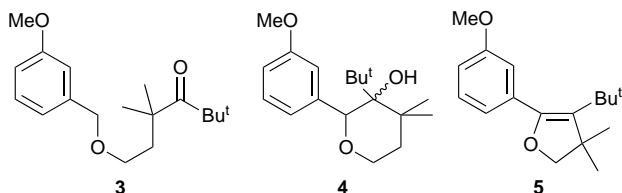
without Wittig rearrangement or decomposition, so long as an electrophile such as a carbonyl moiety exists in a favourable situation, and (ii) the stereoselectivity of cyclization is tightly controlled by the base–solvent system used. The stereoselectivity can probably be rationalized as follows: for the Bu<sup>t</sup>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  $\alpha$ -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<sup>t</sup>OK in THF to give *trans*-**2a** exclusively (room temp. for 4.5 h; 87%).

Since the substrate **1** lacks a  $\beta$ -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  $\beta$ -hydrogens on the alkyl chain. Treatment of **3** with LDA in THF (–78 °C to room



temp.) gave the expected cyclization product **4** in high yield,<sup>‡</sup> while the use of Bu<sup>t</sup>OK–DMSO induced almost no reaction. Thus, intramolecular nucleophilic addition of the  $\alpha$ -carbanion of an alkyl benzyl ether to the carbonyl of the alkyl site takes place effectively even if it bears  $\beta$ -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<sup>7§</sup> in high yield upon treatment with SOCl<sub>2</sub> 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  $\alpha$ -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<sup>0</sup> (ref. 7). However, this method is expensive and not suitable for large-scale synthesis.

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