

One-carbon ring-expansion of 2-substituted cyclohexanones via lithium- and magnesium β -oxido carbenoid rearrangement: a new synthesis of 2,7-disubstituted and 2,2,7-trisubstituted cycloheptanones

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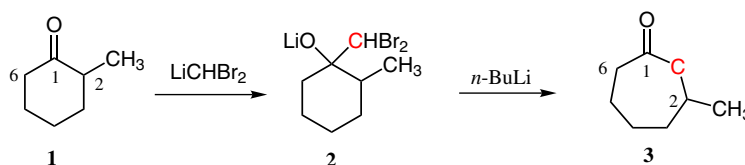
Abstract—Lithium α -sulfinyl carbanion of 1-chloroethyl *p*-tolyl sulfoxide was reacted with 2-substituted cyclohexanones to afford adducts in good yields. The adducts were treated with LDA or *t*-BuMgCl to give lithium or magnesium alkoxides, which were treated with *t*-BuLi or *i*-PrMgCl to afford one-carbon ring-expanded 2,7-disubstituted cycloheptanones through β -oxido carbenoids. Interestingly, 2,3-disubstituted cycloheptanones were obtained in a trace amount or were not obtained at all. The enolate intermediates of this reaction were found to be able to get trapped with electrophiles to give 2,2,7-trisubstituted cycloheptanones in moderate to good yields. This method is very useful for the synthesis of 2,7-disubstituted cycloheptanones and 2,2,7-trisubstituted cycloheptanones from 2-substituted cyclohexanones in only two steps.

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One-carbon homologation of cyclic ketones via β -oxido carbenoid rearrangement is one of the most useful and reliable methods for one-carbon ring enlargement.¹ A few methods have been reported so far from Normant,² Kobrich,³ Yamamoto,⁴ Hiyama,⁵ Cohen,⁶ and by us.⁷ In these reports, Yamamoto's group investigated their chemistry with 2-methylcycloalkanones. For example, treatment of the product **2**, derived from the addition reaction of 2-methylcyclohexanone **1** with dibromomethyl lithium, with *n*-BuLi in ether at -95°C gave 3-methylcycloheptanone **3** in good yield with 97% selec-

tivity (Scheme 1).^{4c,d} The product **3** was derived from the one-carbon insertion between C₁ and C₂ carbons by the β -oxido carbenoid rearrangement. As the β -oxido carbenoid rearrangement is classified as nucleophilic rearrangement similar to the Baeyer–Villiger oxidation,⁸ rearrangement of a more substituted carbon (C₂-carbon) was quite consistent with the tendency of the rearrangement.

Hiyama reported selective olefinic carbon migration in his synthesis of nootkatone using β -oxido carbenoid



Scheme 1. Yamamoto's one-carbon ring-expansion of 2-methylcyclohexanone by β -oxido carbenoid rearrangement with dibromomethyl lithium as a one-carbon unit.

Keywords: Sulfoxide; β -Oxido carbenoid rearrangement; One-carbon ring-expansion; 2,7-Disubstituted cycloheptanone; 2,2,7-Trisubstituted cycloheptanone.

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rearrangement as the key reaction.⁵ Cohen and co-workers also reported the migration of a more highly substituted alkyl group in his carbenoid-type base-induced ring expansion.⁶

We recently reported one-carbon ring-expansion of symmetrical cyclic ketones through β -oxido carbenoids which were generated by the sulfoxide–metal exchange reaction of β -hydroxy α -chloroalkyl aryl sulfoxides.^{7e} As a development of our method for the one-carbon ring-expansion, we studied the expansion of several unsymmetrical cycloalkanones, 2-substituted cyclohexanones **4**, through the adduct with 1-chloroethyl *p*-tolyl sulfoxide **5** and quite interesting results were obtained (Scheme 2).

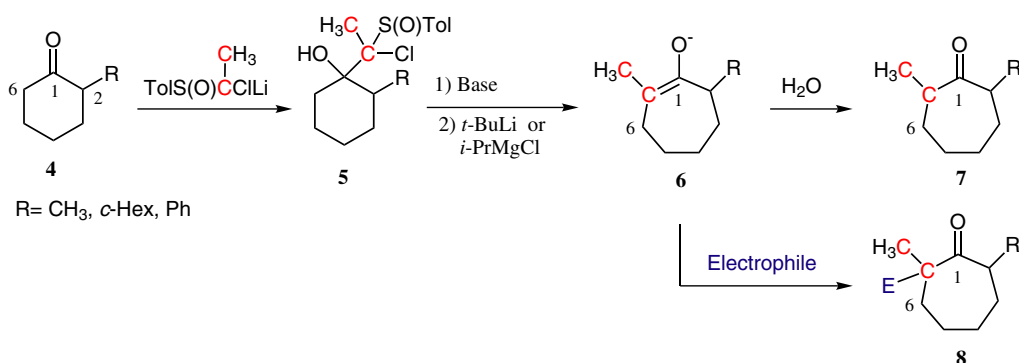
The rearrangement gave 2,7-disubstituted cycloheptanone **7** in high selectivity through enolate **6**. It is worth noting that the one-carbon insertion took place between C₁ and C₆ carbons. The rearrangement is in reverse direction to that of Yamamoto's results (compare the reaction in Scheme 1). In addition, we were able to trap the enolate intermediate **6** with several electrophiles to obtain 2,2,7-trisubstituted cycloheptanones **8**.

At first, 2-cyclohexylcyclohexanone was reacted with lithium α -sulfinyl carbanion of 1-chloroethyl *p*-tolyl sulfoxide at -70°C to give the adduct **9** in 80% yield as a

mixture of two diastereomers (**9**-Main and **9**-Minor) in a ratio of 3:1.⁹ The diastereomers **9** were treated with a base to afford an alkoxide, which was then treated with an alkyl metal. The sulfoxide–metal exchange reaction took place to generate β -oxido carbenoid and one-carbon expanded cycloheptanone **10** was obtained. The results are summarized in Table 1.

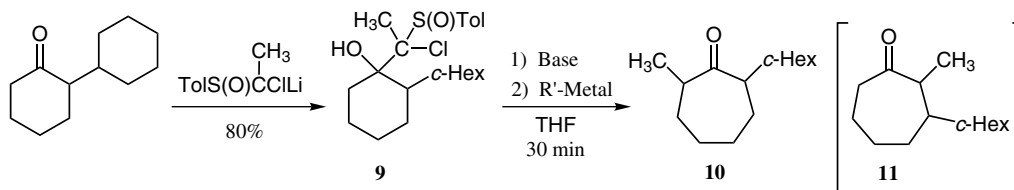
First, **9**-Main was treated with LDA, and the resultant lithium alkoxide was treated with excess *t*-BuLi at -70°C for 30 min (entry 1). We obtained a cycloheptanone derivative as a main product and from detailed inspection of its IR and ¹H NMR, the product was determined to be 2-cyclohexyl-7-methylcycloheptanone **10**. Very interestingly, no 2,3-disubstituted isomer **11** was obtained at all. Entries 2 and 3 show the results of the reaction of magnesium- and aluminum-alkoxide with *t*-BuLi. Both reactions gave **10** as the sole product in over 80% yield.

The reaction of magnesium alkoxide of **9**-Main with *i*-PrMgCl was found not to proceed at -70°C . When this reaction was carried out at 0°C to room temperature, the alkoxide disappeared and **10** was obtained in 10% yield. The main product was 2-cyclohexylcyclohexanone (entry 4). Obviously, a retro aldol-type reaction took place in this reaction. Similar treatment of **9**-Minor with *t*-BuMgCl followed by *t*-BuLi gave again only **10**; how-



Scheme 2.

Table 1. One-carbon ring-expansion of 2-cyclohexylcyclohexanone to 2-cyclohexyl-7-methylcycloheptanone **10**



Entry	9	Base	R'-metal (equiv)	Temperature ($^\circ\text{C}$)	10 ^a /Yield (%)
1	9 -Main	LDA	<i>t</i> -BuLi (4)	-70	62
2	9 -Main	<i>t</i> -BuMgCl	<i>t</i> -BuLi (4)	-70	83
3	9 -Main	Al(CH ₃) ₃	<i>t</i> -BuLi (4)	-70	87
4	9 -Main	<i>t</i> -BuMgCl	<i>t</i> -PrMgCl (2)	0 – rt	10 ^b
5	9 -Minor	<i>t</i> -BuMgCl	<i>t</i> -BuLi (4)	-70	14 ^c

^a A mixture of *cis*/*trans*-isomers.

^b 2-Cyclohexylcyclohexanone (36%) was obtained as a by-product.

^c About 30% of the starting material **9**-Minor was recovered.

ever, the yield was quite low. In this case, the sulfoxide–lithium exchange was found to be slow and the starting material was recovered (entry 5).

The regioselectivity of this reaction is very interesting. A rational explanation of this selectivity is as follows (Fig. 1). By treatment of the magnesium alkoxide **A** with *t*-BuLi, the sulfoxide–lithium exchange reaction took place to afford lithium β-oxido carbenoid **B**. The conformation of the carbenoid would be fixed by the formation of the chelate ring.^{4d} Two configurational isomers of the carbenoids **C** and **D** must be present in equilibrium. The isomer **D** has two bulky substituents (cyclohexyl and methyl groups) close to each other and the steric repulsion forces the equilibrium to **C**. The nucleophilic rearrangement from the isomer **C** must give **10** in high regioselectivity.

We further investigated this chemistry by using 2-methylcyclohexanone derivative **12a** and 2-phenylcyclohexanone **12b** with 1-chloroethyl *p*-tolyl sulfoxide and the results are summarized in Table 2. The addition reaction of lithium α-sulfinyl carbanion with 2-methylcyclohexanone derivative **12a** gave the adduct **13a** in high yield as two diastereomers, **13a-Main** (60%) and **13a-Minor** (35%). The main adduct was treated with *t*-BuMgCl followed by *t*-BuLi at –70 °C for 30 min to give 2,7-di-

methylcycloheptanone derivative **14a** in 65% yield (entry 1). Again, one-carbon insertion took place between C₁ and C₆ carbons and no 2,3-disubstituted cycloheptanone **15a** was obtained.

Entry 2 shows that in this case the rearrangement gave much better yield (83%) with magnesium β-oxido carbenoid. In this reaction, the regioisomer **15a** was obtained in a trace amount (4%). The reaction was carried out with the minor adduct (**13a-Minor**) with *t*-BuLi and *i*-PrMgCl (entries 3 and 4). The sulfoxide–magnesium exchange reaction of **13a-Minor** was found to be sluggish and a much lower yield was obtained; however, the product was again **14a**.

The results starting from 2-phenylcyclohexanone **12b** are summarized in entries 5 and 6. The main adduct **13b-Main** was treated with *t*-BuMgCl followed by *i*-PrMgCl to afford **14b** in 84% yield with 5% of the regioisomer **15b** (entry 5). Again, the sulfoxide–magnesium exchange reaction took place slowly with the minor adduct and the yield of the product was quite low (entry 6).

From the viewpoint of synthetic organic chemistry, trapping of the enolate intermediate of the β-oxido carbenoid rearrangement was quite useful for the synthesis

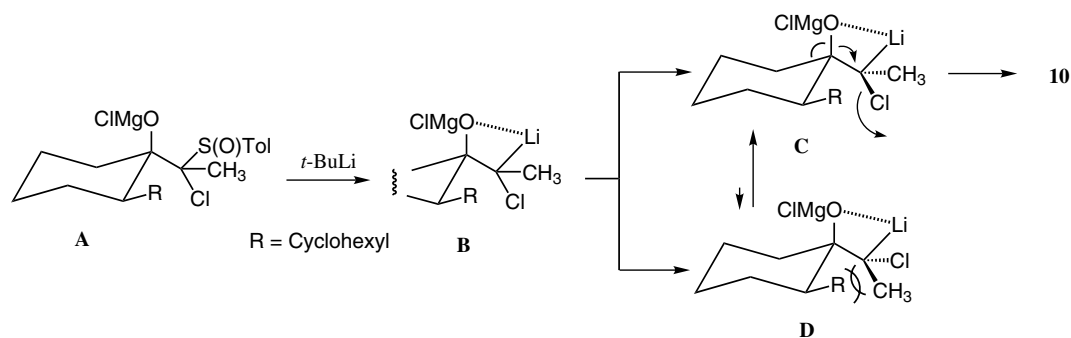
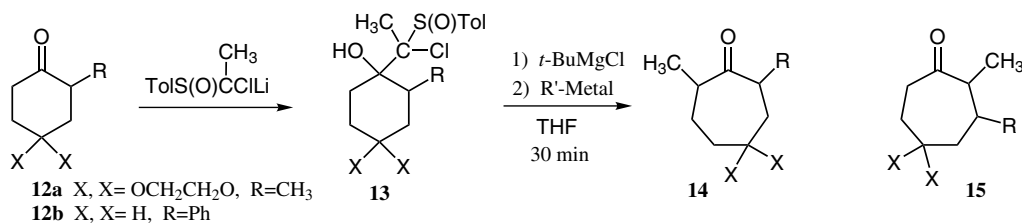


Figure 1. A rational explanation for the selective formation of 2-cyclohexyl-7-methylcycloheptanone **10**.

Table 2. One-carbon ring-expansion of 2-substituted cyclohexanones **12** to 2-methyl-7-substituted cycloheptanones **14**

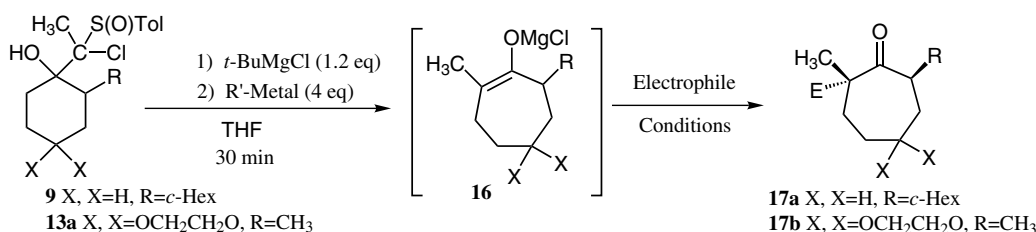


Entry	12	13	R'-metal (equiv)	Temperature (°C)	14 /Yield (%)	15 /Yield (%)
1	12a	13a-Main (60%)	<i>t</i> -BuLi (4)	–70	65	Trace
2		13a-Main	<i>i</i> -PrMgCl (4)	0–rt	83 ^a	4
3		13a-Minor (35%)	<i>t</i> -BuLi (4)	–70	25	0
4		13a-Minor	<i>i</i> -PrMgCl (8)	0–rt	64 ^a	Trace
5	12b	13b-Main (54%)	<i>i</i> -PrMgCl (4)	0–rt	84 ^b	5
6		13b-Minor (30%)	<i>i</i> -PrMgCl (4)	0–rt	10 ^c	0

^a A mixture of two diastereomers (10:1).

^b A mixture of two diastereomers (13:1).

^c About 20% of **13b-Minor** was recovered.

Table 3. One-carbon ring-expansion of 2-cyclohexylcyclohexanone and **12a** to 2,2,7-trisubstituted cycloheptanones **17a** and **17b** through the adducts **9** and **13a**

Entry	9 or 13a	R'-metal	Electrophile	Conditions	E	17 /Yield (%)
1	9 ^a	<i>t</i> -BuLi	CH ₃ OD	−70 °C, 5 min	D	87 ^c
2		<i>t</i> -BuLi	PhCHO	−70 °C, 30 min	PhCH(OH)	82 ^d
3		<i>t</i> -BuLi	PhCOCl	−70 °C, 30 min	PhCO	62 ^c
4		<i>t</i> -BuLi	CH ₃ I ^f	−70 °C–rt, 15 h	CH ₃	49
5	13a ^b	<i>i</i> -PrMgCl	CH ₃ OD	rt, 5 min	D	82 ^c
6		<i>i</i> -PrMgCl	PhCHO	rt, 30 min	PhCH(OH)	75 ^c
7		<i>i</i> -PrMgCl	PhCOCl	rt, 30 min	PhCO	73 ^c
8		<i>i</i> -PrMgCl	CH ₃ I ^f	rt, 15 h	CH ₃	73

^a **9**-Main was used.^b **13a**-Main was used.^c D content 93%.^d A mixture of two diastereomers (7:1).^e Single product was obtained.^f HMPA (4 equiv) was added as an additive.

of multi-substituted carbonyl compounds.^{7d,e} We tried to trap the enolate intermediates of the above-mentioned reactions with several electrophiles and a new method for synthesis of 2,2,7-trisubstituted cycloheptanones from 2-substituted cyclohexanones was realized. The results are summarized in Table 3.

As shown in entry 1, **9**-Main was treated with *t*-BuMgCl followed by *t*-BuLi at −70 °C for 30 min. The reaction was quenched by adding excess CH₃OD to give 7-deuterated ketone in 87% yield with 93% deuterium incorporation (entry 1). Quenching of the reaction with benzaldehyde produced the adduct alcohol in 82% yield (entry 2). In a similar way, the reaction with benzoyl chloride gave diketone in 62% yield (entry 3). When the trapping was carried out with iodomethane, addition of HMPA as an additive was found to be effective to give 2-cyclohexyl-7,7-dimethylcycloheptanone in 49% yield (entry 4). The same reaction was carried out starting from **13a**-Main and the results are shown in entries 5–8. By this method, regioselectively substituted cycloheptanone derivatives having multisubstituents can be synthesized.¹⁰

We are continuing to study the scope and limitations of this procedure and the applications to new synthetic methods, which will be reported in due course.

Acknowledgements

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chloroalkyl *p*-tolyl sulfoxides to carbonyl carbon. Only two diastereomers were obtained although the adducts have four chiral centers. Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130.

10. A synthesis of 4,4-ethylenedioxy-2,7,7-trimethylcycloheptanone (Table 3, entry 8) is reported as a representative example of this method. To a solution of *t*-BuMgCl (0.36 mmol) in 3 mL of dry THF in a flame-dried flask at 0 °C under Ar atmosphere was added a solution of the adduct **13a**-Main (112 mg; 0.3 mmol) in 2 mL of dry THF dropwise with stirring. The reaction mixture was stirred at 0 °C for 10 min. To a solution of the magnesium alkoxide was added *i*-PrMgCl (1.2 mmol) dropwise with stirring. The reaction mixture was slowly allowed to warm to room temperature for 30 min. HMPA (0.21 mL) was added to a

solution of the ring-expanded enolate and stirred for 10 min. Iodomethane (1.2 mmol) was added dropwise to the reaction mixture and the solution was stirred at room temperature for 15 h. The reaction was quenched with satd aq NH₄Cl and the whole was extracted with CHCl₃ and the product was purified by silica-gel column chromatography to afford 4,4-ethylenedioxy-2,7,7-trimethylcycloheptanone (47 mg; 73%) as colorless crystals; mp 36–37 °C (hexane). IR (KBr) 2965, 2875, 1705 (CO), 1458, 1120, 1096, 947, 860 cm⁻¹. ¹H NMR: δ 1.04 (3H, d, *J* = 6.6 Hz), 1.07 (3H, s), 1.11 (3H, s), 1.47–1.59 (3H, m), 1.65–1.78 (2H, m), 2.16 (1H, dd, *J* = 13.5, 12 Hz), 3.11–3.20 (1H, m), 3.89–3.99 (4H, m). MS *m/z* (%) 212 (M⁺, 6), 184 (36), 156 (12), 141 (11), 113 (87), 99 (75), 86 (100). Calcd for C₁₂H₂₀O₃: M, 212.1412. Found: *m/z* 212.1405.