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A new synthesis of α,α-disubstituted carbonyl compounds from carbonyl compounds with one-carbon homologation

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Abstract—Lithium α-sulfinyl carbanions of 1-chloroalkyl *p*-tolyl sulfoxides were reacted with carbonyl compounds to afford adducts in high to quantitative yields. The adducts were treated with *t*-BuMgCl or LDA to give magnesium or lithium alkoxides, which were treated with *i*-PrMgCl or *t*-BuLi to afford the enolate with one-carbon elongation through β-oxido carbenoids. The enolate intermediates were found to be able to be trapped with electrophiles to give α,α-disubstituted carbonyl compounds in moderate to good yields. As a whole, this procedure offers a new and good method for synthesis of α,α-disubstituted carbonyl compounds from carbonyl compounds with one-carbon homologation in only two synthetic steps.

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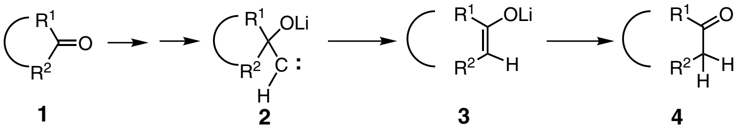
New development of efficient methods for construction of organic compounds with more than two carbon–carbon bond-formations is obviously a most important challenge in synthetic organic chemistry. Tandem or cascade reactions, in which several transformations are operated in a single synthetic step, are examples of one such methodology and have received much attention these days.[1] Another example is the trapping of the reactive intermediate in a reaction with several reagents to get over two carbon–carbon bonds in one flask.

The rearrangement of β-oxido carbenoids **2**, which were derived from carbonyl compounds **1**, is reported to be a useful reaction for one-carbon homologation of carbonyl compounds **1** to **4**, including one-carbon ring-expansion of cyclic ketones (Scheme 1).[2] Nozaki and co-workers and Normant and co-workers used dichloromethyllithium and dibromomethyllithium as a one-carbon homologating agent.[3] Cohen and co-workers used bis(phenylthio)methyllithium,[4] and we used lithium α-sulfinyl carbanion of 1-chloroalkyl aryl sulfoxides as one-carbon homologating agents.[5]

All these reactions were expected to proceed via enolates **3**. If these enolates **3** could be trapped with electrophiles, α-substituted carbonyl compounds would be expected to be produced; however, no such investigations have been reported.

Recently, we reinvestigated our homologation of carbonyl compounds **1** with 1-chloroalkyl aryl sulfoxides **5** as homologating agents.[5] Especially, we focused our attention on trapping the enolate intermediates **8**, which were derived from the adducts **6** via the rearrangement of β-oxido carbenoids **7**, and it was found that the intermediates **8** indeed could be trapped with some



Scheme 1.

Keywords: Sulfoxide; Sulfoxide–metal exchange; β-oxido carbenoid; Homologation; α,α-Disubstituted carbonyl compound.

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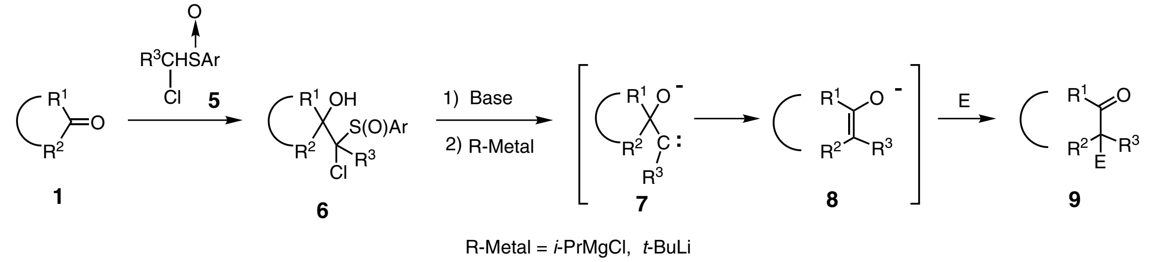


Scheme 2.

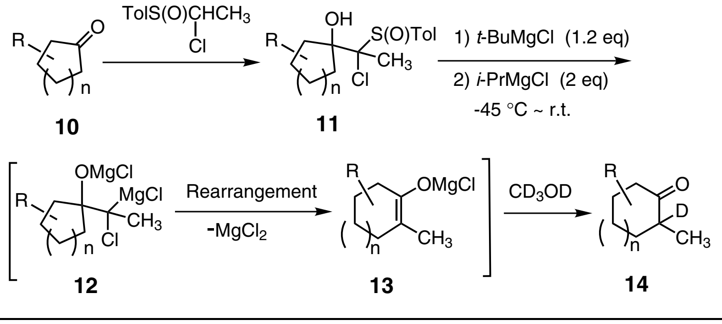
electrophiles to afford the α,α-disubstituted carbonyl compounds **9** with one-carbon homologation (Scheme 2).

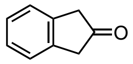
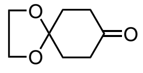
First, we reinvestigated our homologation of ketones **10** through the adducts **11** with various bases and alkylmetals, and the magnesium β-oxido carbenoids **12** were found to give better yields compared with the former conditions (LDA and *t*-BuLi).[5] The representative reaction is as follows (see Table 1). To a solution of the adduct **11**, which was synthesized from ketone **10** and lithium α-sulfinyl carbanion of 1-chloroethyl *p*-tolyl sulfoxide at −70 °C in almost quantitative yield, in THF at −45 °C was added *t*-BuMgCl (1.2 equiv) and the reaction mixture was stirred for 10 min. By this treatment, magnesium alkoxide was formed. To this solution was added 2 equiv of *i*-PrMgCl and the temperature of the reaction mixture was allowed to warm to room temperature. The sulfoxide–magnesium exchange reaction[6] takes place to afford the magnesium carbenoid **12**, which rearranges to the magnesium enolate **13**. Finally, the reaction was quenched by adding excess CD_3OD to give 2-deuterio-2-methylcycloalkanone **14** in good chemical yield. The study was carried out by using six kinds of cyclic ketones and the results are summarized in Table 1.

As shown in Table 1, the adducts **11** derived from 5-membered ketone to 15-membered ketone gave the 2-methylcycloalkanones with one-carbon expansion in 52–82% chemical yields. The results for the quenching of this reaction with CD_3OD are quite interesting. In the cases in entries 1–3 and 6, 2-deuterated cyclic ketones **14** in good to high deuterium incorporation were obtained. No regioisomer was obtained in these cases. From these results it was anticipated that when this reaction is quenched with some electrophiles, 2,2-disubstituted ketones could be obtained. In contrast to these results, the reaction shown in entries 4 and 5 did not give satisfactory deuterium incorporation. The results were found not to be experimental error. We investigated the proton source for these reactions; however, at this time the real reason for this low deuterium incorporation is still obscure.

In any event, several electrophiles were added to the enolate intermediates **13** and the results are summarized in Table 2. We selected three adducts **11**, which were

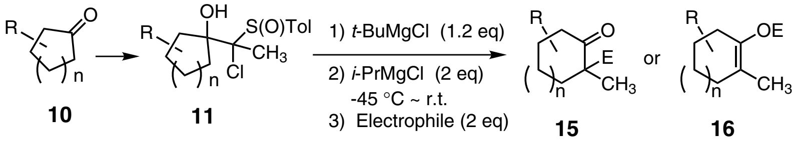
Table 1. Synthesis of 2-deuterio-2-methylcycloalkanones **14** from cycloalkanones **10** with one-carbon homologation

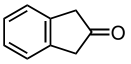
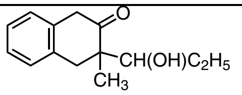
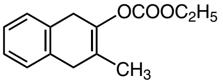
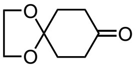
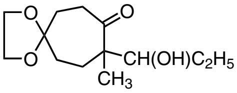
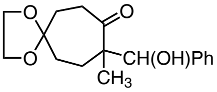
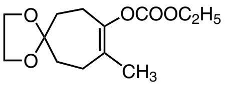
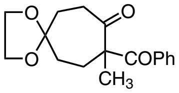
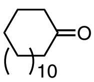
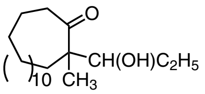
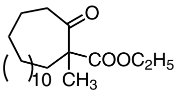
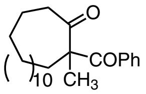


Entry	Cyclic ketone **10**	**14**	
		Yield (%)	D-content (%)[a]
1		70	93
2		75	95
3	Cyclooctanone	54	97
4	Cyclodecanone	52	65
5	Cyclododecanone	82	51
6	Cyclopentadecanone	78	88

[a] The deuterium incorporation was measured by ^1H NMR.

Table 2. Synthesis of 2-methyl-2-(substituted)cycloalkanones **15** and enol carbonates **16** from cycloalkanones **10** with one-carbon homologation

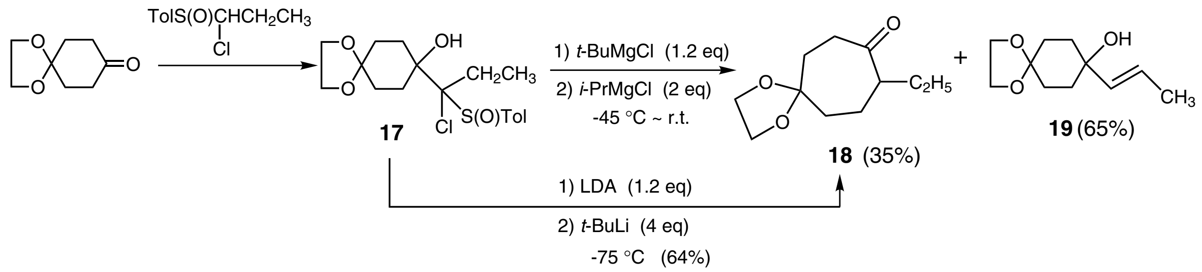


Entry	Cyclic ketone **10**	Electrophile	Product	
				Yield (%)
1		CH_3CH_2CHO	**15a** 	38
2		$ClCOOC_2H_5$	**16a** 	40
3		CH_3CH_2CHO	**15b** 	71
4		PhCHO	**15c** 	40
5		$ClCOOC_2H_5$	**16b** 	74
6		PhCOCl	**15d** 	63
7		CH_3CH_2CHO	**15e** 	73
8		$ClCOOC_2H_5$	**15f** 	33
9		PhCOCl	**15g** 	71

synthesized from 5, 6, and 15-membered cyclic ketones and 1-chloroethyl *p*-tolyl sulfoxide. Propionaldehyde, benzaldehyde, acetone, ethyl chloroformate, and benzoyl chloride were selected as the representative examples for the electrophiles. The two aldehydes reacted with the enolate intermediates to give the adducts **15** (entries 1, 3, 4, and 7); however, the yields were found to be somewhat variable. The reaction with acetone did not give any adduct and only 2-methylcycloalkanones (**15**; E = H) were obtained. Benzoyl chloride was also found to be effective in this procedure to give the benzoylated product in up to 71% yield (entries 6 and 9). The reaction with ethyl chloroformate gave somewhat different results. In case of the reaction with **11** prepared from five and six-membered ketones, the products were found to be the enol carbonates **16a** and **16b**.[7] No expected ketones having ethoxycarbonyl group at the α-position was obtained (entries 2 and 5). However, the reaction with **11** prepared from 15-membered ketone gave the 16-membered ketone having ethoxycarbonyl group at α-position **15f**,[8] though the yield was somewhat low (entry 8).

The results in entries 1 and 2 are quite interesting. If one treats 2-tetralone with a base followed by some electrophiles, the electrophiles must be substituted on the carbon between the carbonyl carbon and the phenyl ring, because the hydrogen on the carbon is more acidic than the hydrogen on the carbon present on the other side of the carbonyl carbon. The compounds **15a** and **16a** in entries 1 and 2 are fairly difficult to synthesize from 2-tetralone by other reactions.

Encouraged by the results described above, we investigated the reaction with 1-chloroalkyl *p*-tolyl sulfoxides having a longer carbon chain other than the methyl group (Scheme 3). The adduct **17**, derived from 1,4-cyclohexanedione *mono*-ethylene ketal and 1-chloropropyl



Scheme 3.

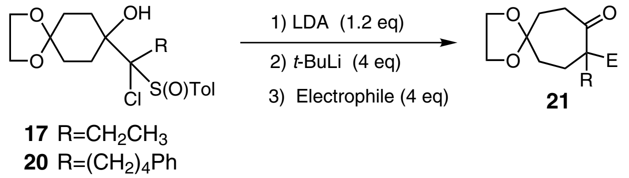
p-tolyl sulfoxide in quantitative yield, was treated under the conditions described in Table 2. However, we obtained the desired product **18** (35%) with an allylic alcohol **19** (65%) as a main product. We applied our former conditions (LDA–*t*-BuLi)[5] and the desired product **18** was obtained in 64% yield.

By using the former conditions,[5] the effect of the alkyl substituents in this procedure was investigated and the results are summarized in Table 3. The adducts **17** having an ethyl group and the adduct **20** having a 4-phenylbutyl group as R were used. As shown by the results in Table 3, entries 1–3, 2,2-disubstituted cycloheptanones having an ethyl group were obtained from 46–64% yields, which indicated the effectiveness of this procedure. However, comparing these results with those in Table 2, entries 3–6, the yields are somewhat lower. In these cases, the reaction with ethyl chloroformate gave the ketones having ethoxycarbonyl group at α-position (**21c** and **21f**) were obtained without the enol carbonates.[9]

Entry 5 in Table 3 shows that the yield of one-carbon expanded 2,2-disubstituted cycloheptanones having a 4-phenylbutyl group was markedly diminished. These results could be explained by the steric hindrance of the 4-phenylbutyl group.

Finally, this procedure was extended to aldehydes (Table 4). The addition reaction of 1-chlorobutyl *p*-tolyl

Table 3. Synthesis of 2-alkyl-2-(substituted)cycloalkanones **21** from the adduct **17** and **20** with one-carbon homologation



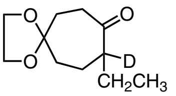
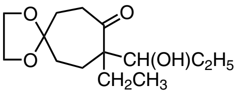
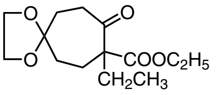
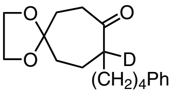
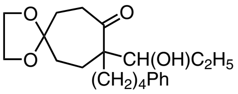
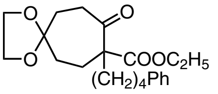
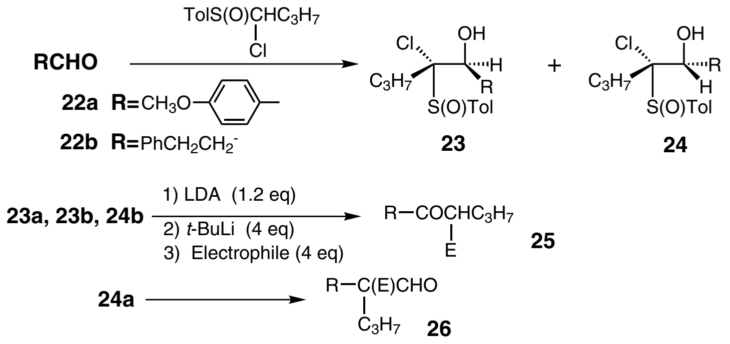
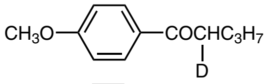
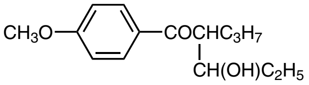
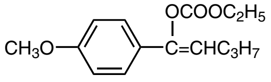
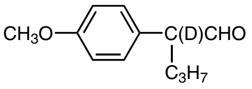
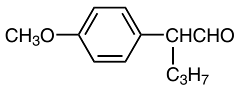
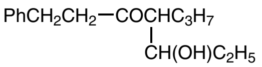
Entry	17 and 20	Electrophile	21	
	R			Yield (%)
1	CH_3CH_2	CD_3OD	**21a** 	64 (D = 99%)
2	CH_3CH_2	CH_3CH_2CHO	**21b** 	61
3	CH_3CH_2	$ClCOOC_2H_5$	**21c** 	46
4	$Ph(CH_2)_4$	CD_3OD	**21d** 	66 (D = 94%)
5	$Ph(CH_2)_4$	CH_3CH_2CHO	**21e** 	13
6	$Ph(CH_2)_4$	$ClCOOC_2H_5$	**21f** 	44

Table 4. Synthesis of α-substituted ketones **25** and α-substituted aldehydes **26** from the adducts **23** and **24** with one-carbon elongation



Entry	Adduct	Electrophile	Product	
				Yield (%)
1	**23a**	CD_3OD		80 (D = 95%)
2	**23a**	CH_3CH_2CHO		75[a]
3	**23a**	$ClCOOC_2H_5$		67[b]
4	**24a**	CD_3OD		76 (D = 82%)
5	**24a**	CH_3CH_2CHO		59
6	**23b**	CH_3CH_2CHO	 $\mathrm{PhCH_2CH_2{-}\underset{\displaystyle CH(OH)C_2H_5}{COCHC_3H_7}}$	54
7	**24b**	CH_3CH_2CHO		65

[a] A mixture of two diastereomers (1:2.3).

[b] A single isomer.

sulfoxide to *p*-anisaldehyde **22a** and 3-phenylpropanal **22b** afforded two adducts **23** and **24** in quantitative yields.[5] In the former study, treatment of **23a** and **24a** with LDA followed by *t*-BuLi gave the ketone **25a** (E = H) and aldehyde **26a** (E = H), respectively, in high stereospecificity.[5] On the other hand, the reaction of both **23b** and **24b** gave ketone **25b** (E = H) in high stereoselectivity.[5]

We tried to trap the enolate intermediate of the reaction of **23a**, **23b**, and **24b** with CD_3OD, propionaldehyde, and ethyl chloroformate (Table 4; entries 1–3, 6, and 7). Quite good results were obtained from the trial and α,α-disubstituted ketones were produced from 54% to 80%. Again, the product in this reaction with ethyl chloroformate was found to be the enol carbonate (entry 3).[10] In contrast to these results, when the reaction of **24a** was quenched with CD_3OD and propionaldehyde, only deuterated aldehyde was obtained in 76% yield (entry 4). The reaction with propionaldehyde did not give the desired adduct but protonated aldehyde **26a** (E = H) was obtained in 59% yield (entry 5).

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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6. (a) Satoh, T. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 481; (b) Satoh, T. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 98.
7. The enol carbonates. **16a**: Colorless oil; IR (neat) 1752 cm^{-1}; ^{13}C NMR δ 153.2 (CO). **16b**: Colorless oil; IR (neat) 1750 cm^{-1}; ^{13}C NMR δ 153.5 (CO).
8. Ketone **15f**: Colorless oil; IR (neat) 1713, 1741 cm^{-1}; ^{13}C NMR δ 173.6 (CO for ester), 207.9 (CO for ketone).
9. The ketones **21c** and **21f**. **21c**: Colorless oil; IR (neat) 1711, 1733 cm^{-1}; ^{13}C NMR δ 172.1 (CO for ester), 209.6 (CO for ketone). **21f**: Colorless oil; IR (neat) 1711, 1732 cm^{-1}; ^{13}C NMR 172.2 (CO for ester), 209.5 (CO for ketone).
10. The enol carbonate in Table 4, entry 3: Colorless oil; IR (neat) 1760 cm^{-1}; ^{13}C NMR δ 159.5 (CO).