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CONJUGATE ADDITION TO α,β-UNSATURATED KETONES WITH MIXED LITHIUM TRIORGANOZINCATES

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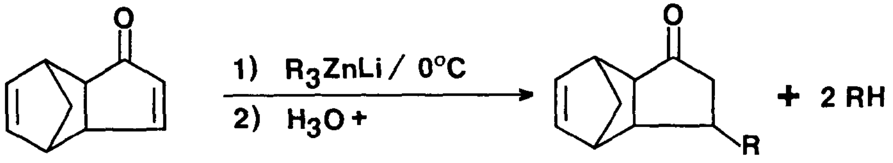
Summary: Lithium Triorganozincates of the type RR'_2ZnLi, where R' = Me and R = n-*Bu or* sec-*Bu, efficiently transfer the R group in a 1,4 fashion to α,β-unsaturated ketones.*

Lithium Triorganozincates (R_3ZnLi)[2,3,4] are known to effect 1,4-addition of alkyl groups to α,β-unsaturated ketones (eq 1 and 2).[4] The solubility and thermal stability of these reagents makes them an attractive alternative to the lithium diorganocuprates (R_2CuLi) which traditionally have been used for this purpose.[5,6] Prior to the present report, however, the use of zincates would result in the loss of two of the three equivalents of the transferring ligand (eq 2) thus making it impractical for achieving the 1,4-addition of any R group that is not readily available because of excessive cost or synthetic difficulties. We report here that mixed zincates of the type RR'_2ZnLi, where R' is methyl, are very effective for circumventing this problem. The R group undergoes efficient 1,4-addition to α,β-unsaturated ketones but the methyl groups (R') remain untransferred.

$$ZnCl_2 + 3\,RLi \xrightarrow{0^\circ C\,/\,THF} R_3ZnLi + 2\,LiCl \qquad (1)$$



(2)

Using the addition of *n*-butyl to cyclohexen-3-one (**3**) as a test case, we initially explored a variety of possible nontransferring ligands (R') as illustrated in eq 3 and 4. The ligands chosen were those which had already proven themselves to be effective in mixed cuprate work. Tetrahydrofuran (THF) was used as the solvent and a 1:1 complex of zinc chloride and N, N, N', N'-tetramethylethylenediamine ($ZnCl_2$•TMEDA)[7] was used as the source of $ZnCl_2$ since it is not hygroscopic and is thus much easier to handle than $ZnCl_2$ itself. Triphenylmethane was used as an indicator.[8] Attempts to employ methoxide (**Ia**),*t*-butoxide (**Ib**), and thiophenoxide (**Ic**) as the nontransferring ligand gave **4** in less than 10% yield. The fact that the indicator turned red after the $ZnCl_2$•TMEDA had been treated with two equivalents of R'Li (**Ia-c**) and one equivalent of *n*-BuLi is consistent with the assumption that the corresponding zincates (**2a-c**) had indeed formed. The use of lithiated 1-hexyne (**Id**) gave none of the desired 1,4-addition product (**4**); in fact, the indicator did not turn red when $ZnCl_2$• TMEDA had been treated with two equivalents of **Id** and one equivalent of *n*-BuLi. In another experiment, however, it was found that the indicator did turn red when an additional two equivalents of *n*-BuLi were subsequently added. Attempts to make a mixed zincate in which R' is cyanide, starting with $Zn(CN)_2$,

$$2R'Li \xrightarrow[\text{THF / 0°C}]{ZnCl_2\cdot TMEDA} R_2'Zn \xrightarrow{n\text{-BuLi}} n\text{-Bu}(R')_2ZnLi \qquad (3)$$

2a-f

1a R' = CH_3O

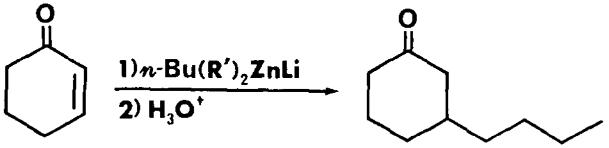
1b R' = $(CH_3)_3O$

1c R' = PhS

1d R' = $CH_3(CH_2)_3C{\equiv}C$

1e R' = Ph

1f R' = CH_3



(4)

3 **4**

were unsuccessful despite the use of a variety of solvents and cosolvents. A 40% yield of **4** was realized when phenyl (**le**) was used as the nontransferring ligand. In contrast to these disappointing results, a nearly quantitative yield of **4** was obtained when methyllithium (**lf**) was used as the source of the nontransferring ligand. The willingness of other groups to transfer preferentially over methyl has been noted in cuprate studies.[6,9]

Several reactions were run in order to outline the scope and limitations of the mixed triorganozincates (see Table). The reaction works well when the transferring ligand is *n*-butyl or *sec*-butyl but not when it is phenyl, vinyl, or *t*-butyl. A further requirement is that the β carbon of the α,β-unsaturated ketone must not be disubstituted. When these criteria are met, however, the reaction is essentially free of 1, 2-addition product and methyl transfer products (see *c* and *d* in Table). It is especially noteworthy that the reaction works well with methyl vinyl ketone inspite of the well known reluctance of this substrate to undergo efficient 1,4-addition. A major advantage of this method is the ease of preparation of the reagent. $ZnCl_2\bullet$ TMEDA itself is readily available[7] and is even stable to many months of atmospheric exposure. The mixed zincate reagents can be prepared at 0° C. Although it is necessary to know the concentration of the MeLi that is used to prepare the RMe_2ZnLi reagents, it is not necessary to know the concentration of the alkyllithium reagent which will be the source of the transferring ligand since an indicator (triphenylmethane in THF or 2, 2'-bipyridine in ether) signals the endpoint in the formation of the RMe_2ZnLi species. Although optimum yields were usually obtained when the enone was added at -78° C, in one case (first entry in the Table) addition of the enone at 0° C led to the highest yield.

In a typical reaction, 1.00 mmol (252 mg) of $ZnCl_2\bullet$ TMEDA and 1 mg of triphenylmethane were dissolved in 5-7 mL THF which was stirring in a flask filled with anhydrous nitrogen. (When reactions were run in ether, a stock solution of $ZnCl_2$ in ether was prepared and 2, 2'-bipyridine was used as the indicator). This solution was cooled to 0° C and 2.00 mmol of methyllithium were added followed by *n*-butyllithium or *sec*-butyllithium until a red color appeared. The ketone (1.00 mmol) was then added at -78° C. (The reaction of *n*-Bu $(Me)_2ZnLi$ with cyclohexen-3-one in THF worked best when the ketone was added at 0° C). The cold bath was removed and the reaction mixture allowed to stir 45 min before being poured into saturated aqueous NH_4Cl and extracted with diethylether.

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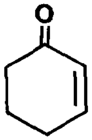
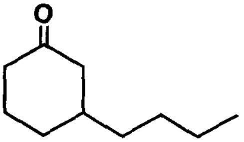
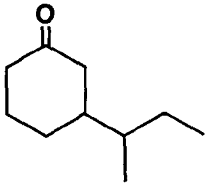
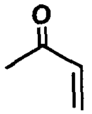
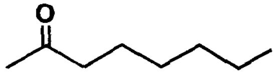
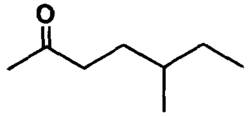
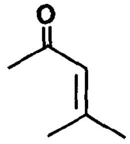
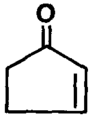
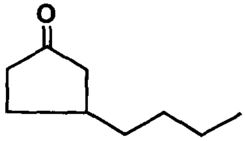
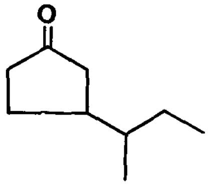
Table. Reactions of RMe_2ZnLi.

Ketone	Conditions	R	Product[a]	Yield,%[b]
	$THF/ZnCl_2\cdot TMEDA$	n-Bu		>98[c]
	ether / $ZnCl_2$	n-Bu		75[c]
	$THF/ZnCl_2\cdot TMEDA$	sec-Bu		83[d,e]
	$THF/ZnCl_2\cdot TMEDA$	n-Bu		80[c]
	ether / $ZnCl_2$	n-Bu		46[c]
	$THF/ZnCl_2\cdot TMEDA$	sec-Bu		88[c]
	$THF/ZnCl_2\cdot TMEDA$	n-Bu	f	
	ether / $ZnCl_2$	n-Bu	f	
	$THF/ZnCl_2\cdot TMEDA$	sec-Bu	g	
	$THF/ZnCl_2\cdot TMEDA$	n-Bu		71[c]
	$THF/ZnCl_2\cdot TMEDA$	sec-Bu		64[c]

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[a] All products were identified by comparing the NMR, IR, and in some cases,mass spectrum with that of authentic samples. [b] Yields were determined by quantitative GC unless otherwise noted. [c] The ratio of the amount of reported product to that of material resulting from 1,4-addition of methyl was>340:1. [d] The ratio of the amount of reported product to that of 3-methylcyclohexanone was 30:1. [e] Yield determined by isolation; see ref. 10. [f] A mixture of products including the 1,2-addition product was obtained. No 1,4-addition of *n*-butyl was detected. [g] Neither 1,4,-nor 1, 2-addition of *sec*-butyl was observed.

REFERENCES AND NOTES

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3. Waack, R.; Doran, M.A. *J. Am. Chem. Soc.* 1963, **85**, 2861-2863.
4. Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* 1977, 679-682.
5. (a) Posner, G.H. *Org. React.* 1972, **19**, 1. (b) Posner, G.H. "An Introduction to Synthesis Using Organocopper Reagents"; John Wiley and Sons, 1980.
6. Numerous improved cuprate reagents and methodologies have been developed. Especially important are higher order, mixed organocuprates derived from CuCN. See Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *J. Org. Chem.* 1984, **49**, 3938-3942 and references therein.
7. Prepared as described in ref. 4. (Five mL TMEDA was added to 10 mL saturated $ZnCl_2$ -THF solution and allowed to stand several hours at room temperature. The crystalline product was filtered and recrystallized from THF; m.p. 177).
8. The preparation of a triorganozincate is facilitated by the use of an indicator to signal the end of the addition of the third equivalent of organolithium to the $ZnCl_2$ or $ZnCl_2$• TMEDA (see ref. 4).
9. Posner, G.H.; Sterling, J.J.; Whitten, C.E.; Lentz, C.M.; Brunelle, D.J. *J. Am. Chem. Soc.* 1975, **97**, 107-118.
10. We thank G.H. Posner for kindly providing spectra of this compound.

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