SUBSTITUTION AND CONJUGATE ADDITION REACTIONS USING NEW LITHIUM TERT-BUTOXY-ALKYLCUPRATE(I) REAGENTS<sup>1</sup>

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Interest in the mechanism and synthetic utility of organocopper reactions is increasing rapidly. The scope and limitations of substitution and conjugate addition teactions using lithium diorganocuprate(I) reagents, R2CuLi, have recently been reviewed. Two significant limitations on the broad utility of these reagents have often been the difficulty in using thermally unstable sec- and tert-alkylcuprates(I)<sup>5</sup> and the need for a large (e.g. 300-500%) excess of organocuprate(I) to achieve complete conversion of substrate to product. 3-5 To circumvent these limitations, we sought a mixed cuprate(I) of the general form (ZCuR) Li in which the group Z would stabilize the reagent containing a sec- or tert-alkyl R group, would allow economical use of this R group, and would simplify product isolation in substitution and conjugate addition reactions. Although several mixed diorganocuprates(I) have recently been studied in different laboratories, 7 none of these reagents is useful for replacement of halogen by sec- or tert-alkyl groups, and no mixed heteroalkyl-alkylcuprate(I) has previously been reported. We selected (ZCuR) Li species wherein Z is R'O initially because some of the corresponding ZCu species are relatively stable: e.g. cuprous tert-butoxide. 8 Now we report that lithium tert-butoxy-sec- and tert-alkylcuprates 1 are easily prepared at low temperature from cuprous tert-butoxide and lithium alkyls and are highly effective and selective in many substitution (Eq. 1a) and conjugate addition (Eq. 1b) reactions even when used in slight (e.g. 20-30%) excess over substrate.

$$\frac{\text{R'X}}{-78^{\circ}} \quad \text{R-R'} \quad \text{(Eq. 1a)}$$

$$\frac{\text{Etrt-BuOCuR}}{\frac{5}{2}} \stackrel{\text{RLi}}{\longrightarrow} \frac{\text{(Eq. 1b)}}{\text{(Eq. 1b)}}$$

The thermal stability of these <u>sec</u>-butyl and <u>tert</u>-butylcuprates 1 in tetrahydrofuran under nitrogen was studied by adding 0.9 equiv of benzoyl chloride to 1.0 equiv of these reagents which had been kept for 1-1.5 hrs at various temperatures and then determining the amount of phenyl alkyl ketone formed. Below -50° the aged cuprates 1 gave phenyl <u>sec</u>-butyl and <u>tert</u>-butyl ketones in high yields, whereas storage of these cuprates 1 at -50° for 1-1.5 hrs apparently causes some decomposition since 5-10% less ketone is produced (<u>i.e.</u>, benzoyl

chloride remains as shown by quenching the reaction mixture with absolute methanol which produces methyl benzoate). Storage at -20° for 1-1.5 hrs causes complete decomposition of cuprates 1.

Table I summarizes the substitution reactions achieved using  $\underline{\text{tert}}$ -butoxy-alkylcuprates  $\underline{1}$  and various acyl and alkyl halides.

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Organic Halide	Reaction Time (min)	Product	R, % Isola <u>tert</u> -Bu	ted Yield <u>sec</u> -Bu
C <sub>6</sub> H <sub>5</sub> COC1	20	C <sub>6</sub> H <sub>5</sub> COR <sup>a</sup>	82	87
Br(CH <sub>2</sub> ) <sub>10</sub> COC1	20	Br(CH <sub>2</sub> ) <sub>10</sub> COR	78 <sup>b</sup>	83
CH <sub>3</sub> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> COC1	20	CH <sub>3</sub> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> COR	61 <sup>c</sup>	66 <sup>C</sup>
n-BuCO(CH <sub>2</sub> ) <sub>4</sub> COC1	20	n-BuCO(CH <sub>2</sub> ) <sub>4</sub> COR	73	86
C6H5CH2Br	240	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> R	88 <sup>c,d</sup>	o <sup>e</sup>
<u>n</u> -C <sub>8</sub> H <sub>17</sub> I	90	<u>n</u> -C <sub>8</sub> H <sub>17</sub> R	82 <sup>c,f</sup>	52 <sup>c,f,g</sup>
<u>n</u> -C <sub>8</sub> H <sub>17</sub> Br	240	$\frac{n-C_8H_{17}R}{}$	83 <sup>d,h</sup>	0 <sup>i</sup>

Table I. Reaction of 1.2-1.3 Equiv of Lithium tert-butoxy-alkylcuprates 1 with 1 Equiv of Organic Halides in THF at -78° (Eq. 1a)

<sup>a</sup>Isobutyrophenone and valerophenone were formed in 80 and 70% yields respectively using lithium tert-butoxy-isopropylcuprate 1 and lithium tert-butoxy-n-butyl-cuprate 1. <sup>b</sup>The yield was increased to 83% when 1.5 equiv of cuprate 1 were used. <sup>c</sup>Yield was determined by quantitative VPC using internal standards. <sup>d</sup>5 Equiv of cuprate 1 were used. <sup>e</sup>90% Bibenzyl. <sup>1</sup>3 Equiv of cuprate 1 were used. <sup>g</sup>After 4 hrs at -78° the reaction was allowed to warm slowly to 0° (½ hrs). <sup>h</sup>-50° Reaction temperature. <sup>1</sup>Starting material was recovered in good yield even after prolonged exposure to cuprate 1.

Several important conclusions can be drawn from the data in Table I: (1) formation of the tert-butoxy-alkylcuprate reagents 1 from equiv amounts of cuprous tert-butoxide and lithium alkyls is complete because no tert-butyl esters 11 and no alcohols 2 are observed; (2) the absence of tert-butyl esters and tert-butyl ethers indicate the specific transfer of only the alkyl group in the tert-butoxy-alkylcuprates 1; (3) replacement of acyl chlorine by a tertiary, or a secondary, or a primary alkyl group can be achieved equally well using the corresponding cuprates 1, but replacement of alkyl halogen is accomplished better with tert-butylcuprate 1 than with sec-butylcuprate 1; (4) n-alkyl ketones can be formed effectively using 1.2-1.3 equiv of tert-butoxy-n-alkylcuprates 1 (see Footnote a in Table I); (5) low temperature (-78°) and short time (20 min) allow conversion of 11-bromoundecanoyl chloride into the corresponding bromoketone (i.e. bromine not replaced by alkyl), whereas higher temperature (-50°) and longer time (4 hrs) effect replacement of bromine by the tert-butyl group. 13,14

It should be noted that <u>trans-l-bromo-2-phenylethylene</u> and l-chloro-1-phenylethane are essentially inert to <u>tert-butylcuprate 1</u> and that 2-octyl iodide and tosylate are converted to 2,2,3-trimethylnonane in less than 25% yield. Thus <u>tert-butyl 1</u> is not useful in substitution of vinylic and secondary alkyl systems.

Conjugate addition of alkenyl groups to  $\alpha,\beta$ -unsaturated carbonyl compounds has most recently been applied to synthesis of various prostaglandins. To explore the potential utility of mixed alkoxy-alkenylcuprates(I) for 1,4 addition reactions, I equiv of cyclo-hexenone was added at -50° to 1.2-1.3 equivs of several tert-butoxy-alkylcuprates 1 in THF to give after 1-3 hrs 3-substituted cyclohexanones in varying isolated yields (2, R = n-Bu, 84%; R = sec-Bu, 77%; R = tert-Bu, 52%; and R = vinyl, low yield 15). Although conjugate addition of primary, secondary, and tertiary alkyl groups is achieved effectively and economically (in terms of the alkyl group) using tert-butoxy-alkylcuprates 1, the low yield of conjugate vinyl adduct is disappointing.

Substitution of alkyl or acyl halogen by a <u>sec-</u> or <u>tert-alkyl</u> group and conjugate addition of such groups is usually best accomplished using organocopper reagents. <sup>3,4</sup> Although the easily prepared <u>tert-butoxy-sec-</u> and <u>tert-alkylcuprates l</u> described herein are thermally unstable above -50°, at or below -50° they are highly effective even when used in slight excess in converting functionalized acid chlorides selectively into the corresponding <u>sec-</u> and <u>tert-alkylketones</u>, in attaching a <u>sec-</u> and <u>tert-alkyl</u> group specifically at the  $\beta$ -carbon of  $\alpha,\beta$ -unsaturated ketones, and in replacing primary alkyl iodide or bromide by the <u>tert-alkyl</u> group. The favorable stoichiometry and functional group specificity of these new alkoxy-alkylcuprate(I) reagents 1 make them welcome additions to the rapidly expanding collection of synthetically useful organometallic reagents. <sup>16</sup>

The chemistry of alkoxy-alkylcuprates(I) is being explored further. 17

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## References

- Part of this work was presented at the 164th National Meeting of the American Chemical Society, New York City, N. Y., August 28 - September 1, 1972, ORGN 159.
- 2. NDEA Fellow 1969-1972.
- 3. G. H. Posner, Org. React., in press.
- 4. G. H. Posner, Org. React., 19, 1 (1972).
- 5. G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, J. Amer. Chem. Soc., 91, 4871 (1969): "For coupling reactions requiring tert-alkyl-copper(I) reagents, lithium di-tert-alkyl(tri-n-butylphosphine)copper(I) compounds are the only practical choice, despite the problems frequently encountered during work-up procedures" (emphasis added).
- In most lithium diorganocuprate(I) reactions, only one of the two R groups in the R<sub>2</sub>CuLi reagent is utilized effectively (see ref 4).

- 7. (a) (RC=C) (alky1)CuLi: J. F. Normant and M. Bourgain, <u>Tetrahedron Lett.</u>, 1970, 2659 and J. F. Normant, Synthesis, 1972, 63;
  - (b) (RC≡C) (alkeny1) CuLi: E. J. Corey and D. J. Beames, <u>J. Amer. Chem. Soc.</u>, <u>94</u>, 7210 (1972);
  - (c) (norbornyl)(butyl)CuLi: G. M. Whitesides, J. San Filippo, Jr., E. R. Stedronsky, and C. P. Casey, ibid, 91, 6542 (1969).
- 8. T. Tsuda, T. Hashimoto and T. Saegusa, J. Amer. Chem. Soc., 94, 658 (1972).
- 9. Complete details of preparation and reactions of these new alkoxy-alkylcuprate reagents will be reported shortly.
- 10. For an earlier report on ketone formation from acid chlorides and organocuprates(I), see G. H. Posner, C. E. Whitten, and P. E. McFarland, J. Amer. Chem. Soc., 94, 5106 (1972)
- 11. Phenoxycopper species have been shown to convert acid chlorides to phenyl esters: T. Kawaki and H. Hashimoto, Bull. Chem. Soc. Japan, 45, 1499 (1972).
- 12. Lithium alkyls react rapidly with even hindered ketones at low temperatures; for the low temperature addition of <u>tert</u>-butyllithium to di-<u>tert</u>-butyl ketone see P. D. Bartlett and E. B. Lefferts, J. Amer. Chem. Soc., 77, 2804 (1955).
- 13. Conversion of acid chlorides to hindered ketones has been reported using tert-butyl-magnesium and tert-butyllithium reagents and cuprous salts as "catalysts".
  - (a) J. E. Dubois, M. Boussu, and C. Lion, Tetrahedron Lett., 1971, 829;
  - (b) J. A. MacPhee and J. E. Dubois, <u>ibid</u>, 1972, 467.
- 14. There is only one reported example of replacement of primary alkyl halogen by a tert-butyl group; that reaction involved a 500% excess of a phosphine complexed lithium di-tert-butylcuprate(I) and a tedious procedure for product isolation (ref 5).
- 15. Cyclohexenone is recovered in >60% yield.
- 16. Using our procedure as described in this communication, Dr. Joel Shulman (The Proctor and Gamble Co., Miami Valley Laboratories) has prepared several isopropyl ketones easily and in high yield from the corresponding acid chlorides and lithium <u>tert</u>-butoxy-isopropylcuprate(I).
- 17. G. H. Posner and J. J. Sterling, J. Amer. Chem. Soc., in press.