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t-BUTOXYMETHYLLITHIUM: DIRECT PREPARATION FROM t-BUTYL METHYL ETHER AND APPLICATIONS AS A HYDROXYMETHYL ANION EQUIVALENT

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Abstract: t-Butyl methyl ether can be metallated directly to afford a reactive and synthetically useful hydroxymethyl anion equivalent.

t-Butyl methyl ether (TBME), a cheap (*ca*. $7/liter) commercial chemical, can be metallated by s-butyllithium - potassium t-butoxide reagent[1] as evidenced by formation of t-butoxyacetic acid upon subsequent treatment with CO_2:

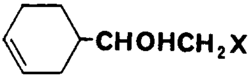
$$t\text{-BuOCH}_3 + s\text{-BuLi/KOtBu} \longrightarrow t\text{-BuOCH}_2\text{Met} \xrightarrow{CO_2} t\text{-BuOCH}_2\,\text{COOH}$$

The metallation takes place readily at -78° using neat TBME (*ca*. 28 equiv), 1 equiv of s-BuLi and 0.7 equiv of KOtBu and after a 2 hr reaction period carbonation affords 75% yield of t-butoxyacetic acid (based on s-BuLi). The active metallating agent is presumably s-BuK.[1] In the case of ketones having alpha hydrogens the reactions of t-$BuOCH_2Met$ formed in this way are complicated by the strongly basic character of the initial mixture, but this problem is readily obviated by the addition of 2 equiv of LiBr in THF solution which precipitates potassium and leaves t-butoxymethyllithium in solution. By this means solutions of the reagent t-$BuOCH_2Li$ in TBME-THF (**1**) can be generated conveniently in one operationally simple step. The foregoing paper describes a general route to alkoxymethyllithium reagents from alkyl chloromethyl ethers.[2] Although this route is applicable to the efficient synthesis of **1**, the direct preparation from TBME discussed herein would appear to be more practical for large scale work with this specific reagent.

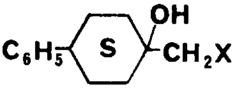
Using a slight excess of the reagent 1 in TBME-THF the following adducts were prepared from the corresponding ketones or aldehydes in the isolated yields indicated in parentheses (X = OtBu). The lower yield obtained with acetophenone was the result of competing enolate formation.

$C_6H_5CHOHCH_2X$

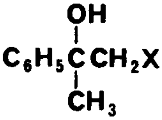
2 (91%)



3 (86%)



4 (93%)

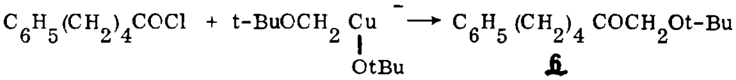


$C_6H_5C(OH)(CH_3)CH_2X$

5 (63 %)

Stannylation of 1 by either trimethyl- or tri-n-butyl-chlorostannane afforded the corresponding t-butyl α-stannyl ether in 94% yield. Benzyl bromide and 1 gave $C_6H_5CH_2CH_2OtBu$ in 83% yield.

The lithium reagent 1 can be utilized for the conversion of acid chlorides to t-butoxymethyl ketones in a single step. Conversion of 1 with 1 equiv of cuprous t-butoxide[3] to the organocopper derivative followed by reaction with 5-phenylpentanoyl chloride provided the t-butoxymethyl ketone 6 in 90% yield.



$$C_6H_5(CH_2)_4COCl + t\text{-}BuOCH_2\underset{\text{OtBu}}{\overset{-}{Cu}} \longrightarrow C_6H_5(CH_2)_4COCH_2Ot\text{-}Bu$$

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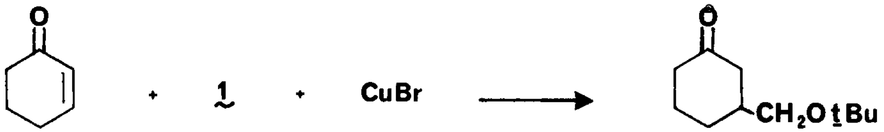
The Gilman reagent from 1 (2 equiv) and CuBr · Me_2S (1 equiv)[4] can be used for the conjugate addition of t-butoxymethyl to α,β-enones. 2-Cyclohexenone, for example, was transformed by reaction with this cuprate at -30° for 40 min to the adduct 7 (90% yield).



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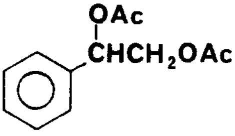
For these C-C bond forming processes to be maximally useful, a satisfactory procedure for cleavage of the t-butyl protecting group is required. Of the methods available for the conversion of t-butyl ethers to alcohols,[5] the method of Ganem proved to be most efficient.[6] Thus, treatment of the various t-butyl ethers (1 mmol) with acetic anhydride (2 ml) and anhydrous ferric chloride (0.05 - 0.1 mmol) at 0° for 15 min afforded the corresponding acetates. For example, this procedure converted 2 to 8 (91%) and 7 to 9 (90%). The acetate ⟶ alcohol transformation is readily effected using potassium carbonate in methanol at 0°.



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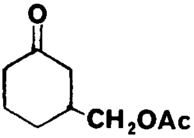

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The ready availability of an equivalent of HOCH$_2^-$ from t-butyl methyl ether in one step should spur synthetic applications of this one-carbon nucleophile. The following section details the experimental procedure for generation of 1.

Conversion of t-Butyl Methyl Ether to t-Butoxymethyllithium (1) and 3. Sublimed and powdered potassium t-butoxide (1.4 mmol) was suspended in 8 ml of dry t-butyl methyl ether[7] under argon. After cooling to -78° the well stirred mixture was treated with 1.4 mmol of s-butyllithium (commercial reagent in cyclohexane solution) over 2 min; an intense yellow-orange color developed. After 2 hr 1.4 ml of 2M LiBr in THF was added and the resulting slurry was stirred at -10° for 30 min, then cooled to -78° and treated with 3-cyclohexene-1-carboxaldehyde (1 mmol). The reaction mixture was quenched after 10 min by addition of aqueous ammonium chloride-ammonia (pH 8) and the reaction product was isolated by extractive workup and chromatography on silica gel to give 153 mg (86.4%) of 3. ^{1}H NMR (CDCl$_3$): 5.65 δ (2H, s), 3.25 - 3.50 (3H, comp. mult.), 2.50 (1H, s), 2.25 - 1.00 (7H, mult), and 1.19 (9H, s). IR (Film): 3470, 3020, 2970, 2910, 2875, 2835, 1650, 1389, 1363, 1199, 1070 cm^{-1}. Mass spectrum (m/e): 198 (M), 141 (M - 57), 111 (M - 87, the t-butoxy methyl radical).[8]

Conjugate Addition of the Gilman Reagent from 1 to 2-cyclohexene-1-one. To a solution of 1 prepared as described above (from 2.17 mmol of s-butyllithium) at -78° was added 159.5 mg of CuBr · Me$_2$S as a solution in 1.1 ml of isopropyl sulfide and 2 ml of TBME. After stirring at -78° for 40 min 2-cyclohexene-1-one (0.705 mmol, 67.8 mg) in 2 ml of TBME was added over 2 min and the mixture was warmed to -30° over 15 min. After 30 min at -30° 2 ml of 1:1 acetic acid-methanol (degassed with argon) was added via syringe and the mixture was immediately poured into 100 ml of aqueous NH$_4$Cl-NH$_3$ (pH 9). Extractive workup afforded 122.6 mg of crude product which after chromatography on silica gel (5% ether/CH$_2$Cl$_2$) gave 81.6 mg of 7 (88% overall); TLC analysis (5% ether/CH$_2$Cl$_2$, 2 developments) shows a single component $R_f = 0.56$. ^{1}H NMR (CDCl$_3$): 3.21 δ (2H, d), 1.0 - 2.4 (mult. 9H), 1.13 (9H, s). IR (CHCl$_3$): 3690, 3620, 3450, 3020, 2980, 2935, 2870, 2440, 2400, 1705, 1365, 1230, 1090, 1060, 910, 760, 670 cm^{-1}. Mass spectrum (m/e) (20 eV.): 184 (M), 169 (M - 15), 127 (M - 57), 111 (M - t-butoxide), 98 (M - t-butoxy methyl radical, 87).

References and Notes

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7. Commercial TBME may be dried by distillation from sodium - benzophenone ketyl.
8. This research was assisted financially by a grant from the National Science Foundation.

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