Synthetic Applications of Gilman Reagents Derived from 2-Bromo-2-cycloalken-1-one Ethylene Ketals[§]

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Abstract: Gilman reagents derived from 2-bromo-2-cycloalken-1-one ethylene ketals react with allylic, propargylic or benzylic halides to produce functionalized 1,4-dienes while reaction with Michael acceptors gives 1,4-adducts.

In 1978, Smith and co-workers reported that the vinyllithium reagent derived from the transmetallation of 2-bromo-2-cyclohexen-1-one ethylene ketal underwent smooth alkylation with a variety of alkyl halides and carbonyl compounds.¹ This was believed to represent a general solution for the construction of α -substituted α,β -unsatured cycloalkenones.² However, in conjunction with a total synthesis of lycopodine, Kraus and co-workers observed that the coupling of a similar species (i.e., 1) with allyl bromide furnished only ketal 2 (Scheme 1).³ We also encountered difficulties in attempts to prepare 1,4-dienes by coupling an α -ketovinyl anion equivalent with functionalized allylic iodides. More importantly, Smith's procedure calls for the use of a 3-5 fold excess of the electrophile, which is undesirable when expensive or complex electrophiles are used. Here we report that mixed cuprates (Gilman reagents) derived from 2-bromo-2-cycloalken-1-one ethylene ketals are useful for cross-coupling reactions or enone conjugate additions.⁴



The Gilman reagents produced with either phenylthic copper (reagent A)⁵ or 3-methyl-3-methoxy-1-butynyl copper (reagent B)⁶ were reacted with allyl bromide (Table 1), both affording the desired allylated product.⁷ In general Corey's ligand (B) gave better yields and required less of the vinylating agent than the phenylthic ligand. Moreover, the organolithium reagents prepared from either 2-bromo-2cyclohepten-1-one ethylene ketal or 2-bromo-2-cycloocten-1-one ethylene ketal were prone to rapid decomposition; hence, the low coupling yields.

The reactions shown in Chart 1 indicate the effectiveness and versatility of this procedure. Allylic, benzylic and propargylic halides⁸ undergo displacement in good yields (entries 7 - 11). Additionally, allyl acetate (12) was also a useful electrophile Transfer of the alkenyl group also occurs with less reactive



alkyl halides, such as <u>n</u>-butyl iodide or bromo acetaldehyde diethyl acetal.⁹ One of the most useful applications of organocopper reagents is in the transformation of acyl halides into ketones,¹⁰ yet the reaction of acetyl chloride with cuprate 4 proceeds in poor yield. As one would expect these reagents add in conjugate fashion to Michael acceptors, such as cyclohexenone or diethyl acetylenedicarboxylate. The limitations of these cuprates are presented in reference 11.



Chart 1 continued



Scheme 2 presents a synthetic application of this methodology. Coupling of the cuprate 3 with iodide 18^{12} permits the facile construction of 21, a potential pseudoguaianolide precursor.¹³ Other applications are forthcoming.

Scheme 2



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- 4. a) The spectroscopic data obtained for all new compounds were fully consistent with the assigned structures. b) Reaction conditions have not been optimized. c) All yields are isolated yields.
- 5. For the addition of $[\alpha$ -(alkoxycarbonyl)vinyl]cuprates to allylic halides and ketones, see: a) Grieco, P. A.; Wang, C.-L. J.; Majetich, G. J. Org. Chem. 1976, 41, 726. b) Marino, J. P.; Floyd, D. M. Tetrahedron Lett 1975, 3897.
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- 7. The following is a typical experimental procedure: To a solution of 3-methoxy-3-methyl-1-butyne (74 mg, 0.75 mmol) in THF (3 mL) was added n-BuLi (0.75 mmol) dropwise at 0°C and stirred for 10 min. The resulting acetylide anion was added to a stirred suspension of CuI (150 mg, 0.75 mmol) in THF (3 mL) at 0°C and stirred at 0°C for 30 min. This solution was added dropwise (via a cannula) to a solution of 2-lithio-2-cyclopenten-1-one ethylene ketal^{2a} (0.75 mmol) in 5 mL of THF at -78°C and stirred 30 min at -78°C. To this mixture (at -78°C) was added dropwise a solution of 4-(trimethylsilyl)-2-butynyl iodide (7)8 (0.19 g, 0.75 mmol) in THF (2 mL). The reaction mixture was slowly warmed to -35°C (1 h) and stirred at -35°C for 6 h. The reaction was quenched by the addition of 1 mL of saturated aqueous ammonium chloride. Standard ethereal workup gave an oil. Chromatography on silica gel provided 490 mg (79%) of coupled material which was homogeneous by TLC analysis and spectral analysis. See ref. 5a for a typical phenylthio cuprate experimental.
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- 11 Cuprates 3 and 4 failed to react with the following electrophiles: cyclohexene oxide, 1,2epoxybutane, cyclohexyl iodide, 4-bromo-1-butene and 4-iodo-2-methyl-1-butene. Shown below are two allylic acetates which also failed to react with both cuprates as well as two Michael acceptors which did not undergo addition / elimination reactions



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