

Organocopper Reagents that Behave as Functionalized Acyl Anions

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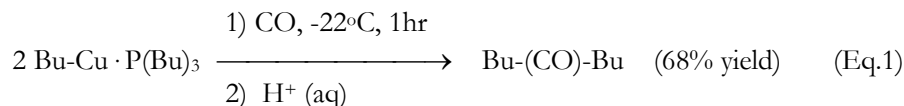
Abstract

The development of acyl anions as synthetic reagents has always been an important goal in organic chemistry. We wish to report examples of functionalized organocopper reagents, produced by the methods of Rieke (Rieke, 1989) and Ebert (Ebert et al., 2005) that have been successfully carbonylated and cross-coupled with alkyl halides to produce functionalized ketones. Although the yields are somewhat low in this initial, exploratory research, the feasibility of this approach is demonstrated. The full potential of this methodology has yet to be determined.

Keywords: Organocopper, Organocuprate, Acyl Anion, Cross-Coupling, Carbonylation, Functionalization

1. Introduction

Developing acyl anions as synthetic reagents has always been a significant goal in organic chemistry (Carey et al., 1990). One approach to such reagents is the carbonylation of organometallic compounds to produce acyl anions. In 1972 Jeffery Schwartz reported the successful carbonylation of alkylcopper reagents, which upon quenching with dilute aqueous acid, produced symmetrical ketones (Schwartz, 1972), (Eq 1).

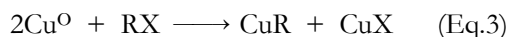
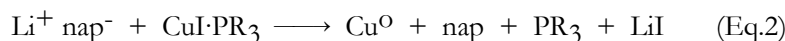


Since that time, there have been many reports of several types of organocopper compounds that have been successfully carbonylated and subsequently cross-coupled with a variety of reagents to produce acylated products (Seyferth & Hui, 1985), (Lipshutz & Elworthy, 1990), (Kabalka et al., 1997). Unfortunately, very little functionality can be incorporated into the organocopper reagents, themselves, due to the organolithium and Grignard precursors most commonly used to produce them.

2. Background

Active Copper and the Direct Formation of Functionalized Organocopper Reagents

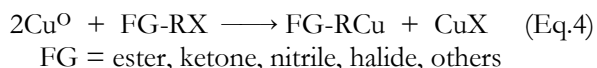
Rieke and Ebert have developed a highly active copper, which allows the direct formation of a wide variety of organocopper reagents from the respective organic halides without utilizing traditional organolithium or Grignard precursors (Rieke, 1989), (Rieke et al., 1989), (Ebert & Rieke, 1984), (Ebert & Rieke, 1988), (Ebert & Klein, 1991), (Ebert et al., 1992), (Ginah et al., 1990). This activated copper is formed by reducing, under argon, an ethereal solution of $\text{CuI} \cdot \text{PR}_3$ with an ethereal solution of preformed lithium naphthalenide or biphenylide. The resulting copper is sufficiently reactive to allow direct oxidative addition to alkyl and aryl halides (Eqs 2 and 3).



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This approach allows the incorporation of functional groups into the organocopper reagents, which would otherwise be prohibited due to the highly reactive organolithium and Grignard precursors (Ginah et al., 1990), (Ebert & Klein, 1991), (Ebert et al., 1992), (Eq 4).



In more recent work, we have successfully carboxylated these functionalized organocopper reagents (Ebert et al., 2005), (Eq. 5).



3. Results and Discussion

Encouraged by our success in the carboxylation of functionalized organocopper compounds, we turned our attention to the carbonylation of these reagents (Eq.6), (Table 1). In the published carbonylation work of Schwartz, no results were reported using aryl halides. We found that, with slight modification, his approach to producing symmetrical aliphatic ketones can be applied to aromatic compounds. When CO is bubbled through a solution of PhCu·P(Bu)₃ for 1hr. at 0°C, and then heated to 60°C for 1hr., followed by quenching with a dilute HCl, benzophenone was produced in a 56% yield (Ebert & Ebert, 2019), (entry 1). In the next entry (entry 2) CH₃CH₂CH₂Cu·P(Bu)₃, produced from CH₃CH₂CH₂Br by the methods of Rieke and Ebert, was treated with CO and subsequently quenched with dilute HCl as described by Schwartz. The yield of the symmetrical ketone 4-heptanone was found to be 35%. This reaction demonstrates that organocopper reagents formed from activated copper can also undergo carbonylation and subsequent conversion into symmetrical ketones. We then explored the possibility of producing functionalized organocopper reagents that could be cross-coupled with alkyl halides after carbonylation. In the next three reactions functionality was incorporated into the organocopper reagents (entries 3-4), or the cross-coupling alkyl halide (entry 5). Although the yields are low, these reactions show this approach's feasibility in producing functionalized organocopper reagents that behave as acyl anions. Interestingly, when attempting to produce the symmetrical ketone from ethyl 3-bromopropanoate, only a low yield (11%) of the homocoupled organocopper reagent, diethyl adipate, was observed (entry 6). None of the symmetrical ketone, diethyl 4-oxopimelate, was detected. In the final entry shown (entry 7) an attempt was made to perform a conjugate addition reaction of a functionalized, carbonylated, organocopper reagent with methyl vinyl ketone. Only a small trace of the conjugate addition product was detected (<3%).

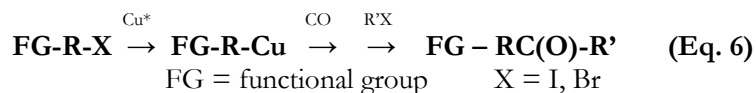


Table 1. Reactions of Carbonylated Organocopper Reagents

Entry	Yield
$(1) \quad 2 \text{ Ph-Li} \xrightarrow[0^\circ\text{C, 15 min.}]{\text{CuI}\cdot\text{P}(\text{Bu})_3} \xrightarrow[1 \text{ hr}]{\text{CO}, 0^\circ\text{C}} \xrightarrow[2 \text{ hr}]{\text{heat}, 60^\circ\text{C}} \xrightarrow{\text{H}^+(\text{aq})} \text{Ph}(\text{CO})\text{-Ph}$	(56 %)
$(2) \quad 2 \text{ CH}_3\text{CH}_2\text{CH}_2\text{Br} \xrightarrow[0.25 \text{ hr}]{\text{Cu}^*, -78^\circ\text{C}} \xrightarrow[1 \text{ hr.}]{\text{CO}, -22^\circ\text{C}} \xrightarrow{\text{H}^+(\text{aq})} \text{CH}_3\text{CH}_2\text{CH}_2(\text{CO})\text{CH}_2\text{CH}_2\text{CH}_3$	(35 %)

<u>Entry</u>					<u>Yield</u>	
(3)	Cl-(CH ₂) ₄ -Br	$\xrightarrow[-70^{\circ}\text{C}, 0.5 \text{ hr.}]{\text{Cu}^*}$	$\xrightarrow[-70^{\circ}\text{C}, 1 \text{ hr.}]{\text{CO}}$	$\xrightarrow[-65^{\circ}\text{C}, 1 \text{ hr.}]{\text{CH}_3\text{I}}$	$\xrightarrow{\text{H}^+ (\text{aq})}$ CH ₃ (CO)CH ₂ CH ₂ CH ₂ CH ₂ Cl	(10%)
(4)	BrCH ₂ COOEt	$\xrightarrow[-78^{\circ}\text{C}, 0.5 \text{ hr.}]{\text{Cu}^*}$	$\xrightarrow[-70^{\circ}\text{C}, 1 \text{ hr.}]{\text{CO}}$	$\xrightarrow[-70^{\circ}\text{C}, 1 \text{ hr.}]{\text{CH}_3\text{I}}$	$\xrightarrow{\text{H}^+ (\text{aq})}$ CH ₃ (CO)CH ₂ COOEt	(12%)
(5)	CH ₃ CH ₂ Br	$\xrightarrow[-70^{\circ}\text{C}, 0.5 \text{ hr.}]{\text{Cu}^*}$	$\xrightarrow[-70^{\circ}\text{C}, 1 \text{ hr.}]{\text{CO}}$	$\xrightarrow[-70^{\circ}\text{C to } -40^{\circ}\text{C}, 1 \text{ hr.}]{\text{CH}_2=\text{CHCH}_2\text{Br}}$	$\xrightarrow{\text{H}^+ (\text{aq})}$ CH ₃ CH ₂ (CO)CH ₂ CH=CH ₂	(20%)
(6)	EtOOCCH ₂ CH ₂ Br	$\xrightarrow[-78^{\circ}\text{C}, 0.5 \text{ hr.}]{\text{Cu}^*}$	$\xrightarrow[-22^{\circ}\text{C}, 1 \text{ hr.}]{\text{CO}}$	$\xrightarrow{\text{H}^+ (\text{aq})}$	EtOOCCH ₂ CH ₂ CH ₂ CH ₂ COOEt	(11%)
(7)	CH ₃ CH ₂ Br	$\xrightarrow[-70^{\circ}\text{C}, 0.5 \text{ hr.}]{\text{Cu}^*}$	$\xrightarrow[-70^{\circ}\text{C}, 0.75 \text{ hr.}]{\text{CO}}$	$\xrightarrow[1) -70^{\circ}\text{C}, 1 \text{ hr.}, 2) -40^{\circ}\text{C}, 1 \text{ hr.}]{\text{CH}_2=\text{CH}(\text{CO})\text{CH}_3}$	$\xrightarrow{\text{H}^+ (\text{aq})}$ CH ₃ CH ₂ (CO)CH ₂ CH ₂ (CO)CH ₃	(<3%)

4. Conclusion

In conclusion, we have shown that the Swartz protocol for converting alkylcopper tri-*n*-butylphosphine complexes into symmetrical ketones can also be expanded to include arylcopper complexes. In addition, with this initial, exploratory, research, we have provided examples of functionalized organocopper reagents that have been subsequently carbonylated and then cross-coupled with alkyl halides. Although the yields reported are somewhat low, the feasibility of this approach has been demonstrated. The full potential of this methodology has yet to be determined.

5. Experimental

5.1 General Procedures

Our basic laboratory procedures, experimental setup, method of gas chromatography analysis, formation of lithium naphthalenide and lithium biphenylide, and formation of CuI·P(Et)₃ and CuI·P(*n*-Bu)₃ have all been previously reported in detail. (Ebert & Rieke, 1984), (Ebert & Rieke, 1988), (Ginah et al., 1990), (Ebert & Klein, 1991), (Ebert et al., 2005).

5.2 Analysis

Aliquots (2 mL) were removed from the reaction vessel at timed intervals and quenched with H₂SO₄ (0.1M, 0.5 mL). The organic layer was analyzed by GC and MS. The compounds were identified by their GC and mass spectra analyses when compared to authentic samples of the products. Yields were determined by GC analysis using the internal standard method and authentic product samples to determine the response factors. All compounds synthesized in this work have been previously reported in the literature. Authentic samples of the products can be purchased commercially or synthesized by published procedures.

5.3 Starting Materials

All starting materials were commercially purchased as reagent grade or better and used as received.

5.4 Formation of Activated Copper

Lithium naphthalenide or lithium biphenylide was prepared as previously reported (Ebert & Rieke, 1984). A second reaction flask was prepared according to the experimental setup and charged with $\text{CuI}\cdot\text{P}(n\text{-butyl})_3$ (10 mmol) and THF or DME (5-10 mL), and the solution gently swirled to dissolve the salt. The copper salt solution was drawn into a syringe and quickly injected into the stirring solution of preformed lithium biphenylide or lithium naphthalenide. After 5 min. the brownish-red suspension of active copper was ready for subsequent reaction.

5.5. Benzophenone (entry 1)

The experimental setup and synthetic procedure is similar to that of Schwartz (Schwartz, 1972). $\text{CuI}\cdot(n\text{-butyl})_3$ (10 mmol) was dissolved in THF (15 mL) in a reaction flask. The temperature was lowered to 0°C and PhLi added (10 mmol) along with a GC internal standard (decane, 2 mmol). The solution was stirred for 15 min. and developed a green tinge. The temperature was held at 0°C for 1 hr. while CO was bubbled through the reaction mixture. The reaction was then heated to 60°C for 2 hrs. after which the reaction was quenched with dilute H_2SO_4 . A sample of the reaction mixture was withdrawn, submitted to GC analysis and compared to an authentic sample of benzophenone purchased from the Sigma-Aldrich Chemistry Company. The MS analysis matched that of the publish spectrum (John Wiley & Sons, Inc.; Spectrum ID: ID_WID-DLO-074159-3). Benzophenone was produced in a 56% yield.

5.6. 4-Heptanone (entry 2)

Activated copper (10 mmol) was formed in a reaction vessel after which the temperature of the solution was lowered to -78°C . 1-Bromopropane (5 mmol) was syringed into the flask along with the GC internal standard (decane, 2 mmol) and allowed to react for 15 min. The temperature was raised to -22°C and CO bubbled through the reaction mixture for 1hr. The reaction was quenched with dilute H_2SO_4 . A sample of the reaction mixture was withdrawn, submitted to GC analysis, and compared to an authentic sample of 4-heptanone purchased from the Sigma-Aldrich Chemistry Company. The MS analysis matched that of the publish spectrum (John Wiley & Sons, Inc.; Spectrum ID: ID_WID-DLO-069596-5). 4-Heptanone was produced in a 35% yield.

5.7. 6-Chloro-2-hexanone (entry 3)

Activated copper (10 mmol) was formed in a reaction vessel after which the temperature of the solution was lowered to -70°C . 1-Bromo-4-chlorobutane (5 mmol) was syringed into the flask along with the GC internal Standard (octane, 2.5 mmol). The solution was stirred for 30 min. to produce the organocopper reagent. Then CO was bubbled through the reaction mixture for 1hr. The temperature was raised to -65°C and Methyl Iodide (15 mmol) was added and the solution stirred for 1hr. The reaction was quenched with dilute H_2SO_4 and A sample of the reaction mixture was withdrawn, submitted to GC analysis, and compared to an authentic sample of 6-chloro-2-hexanone purchased from the Sigma-Aldrich Chemistry Company. The MS analysis matched that of the published spectrum (Murphy, et al., 2005). 6-Chloro-2-hexanone was produced in a 10% yield.

5.8. Ethyl Acetoacetate (entry 4)

Activated copper (10 mmol) was formed in a reaction vessel after which the temperature of the solution was lowered to -78°C . Ethyl 2-Bromoacetate (5 mmol) and the GC internal Standard (octane, 2.5 mmol) were injected into the flask. The solution was stirred for 30 min. to produce the organocopper reagent. Then CO was bubbled through the reaction mixture for 1 hr. at -70°C . Methyl Iodide (15 mmol) was added and the solution stirred for 1hr. The reaction was quenched with dilute H_2SO_4 and a sample of the reaction mixture was withdrawn, submitted to GC analysis, and compared to an authentic sample of ethyl acetoacetate purchased from the Sigma-Aldrich Chemistry Company. The MS analysis matched that of the publish spectrum (John Wiley & Sons, Inc.; Spectrum ID: ID_WID-DLO-070638-7). Ethyl acetoacetate was produced in a 12% yield.

5.9. 5-Hexen-3-one (entry 5)

Activated copper (10 mmol) was formed in a reaction vessel after which the temperature of the solution was lowered to -70°C . Ethyl bromide (5 mmol) was syringed into the flask along with the GC internal Standard (decane,

2 mmol). The solution was stirred for 30 min. to produce the organocopper reagent. Then CO was bubbled through the reaction mixture for 1hr. at -70°C . Allyl bromide (15 mmol) was added and the solution stirred for 1hr. as the temperature was allowed to slowly rise to -40°C . The reaction was quenched with dilute H_2SO_4 and a sample of the reaction mixture was withdrawn and submitted to GC analysis. For comparison, an authentic sample of the compound can be synthesized by the method of Le Roux and Dubac (Le Roux & Dubac, 1996).

The MS analysis matched that of the published spectrum (John Wiley & Sons, Inc.; Spectrum ID: ID_WID-DLO-001514-5). 5-Hexen-2-one was produced in a 20% yield.

5.10. Diethyl 4-oxopimelate/(diethyl adipate) (entry 6)

Activated copper (10 mmol) was formed in a reaction vessel after which the temperature of the solution was lowered to -78°C . Ethyl 3-bromopropanoate (5 mmol) and the GC internal standard (decane, 2 mmol) were injected into the flask. The solution was stirred for 30 min. to produce the organocopper reagent. Then CO was bubbled through the reaction mixture for 1hr. at -22°C . The reaction was quenched with dilute H_2SO_4 . A sample of the reaction mixture was withdrawn, submitted to GC analysis, and compared to authentic samples of 4-oxopimelate and diethyl adipate purchased from the Sigma-Aldrich Chemistry Company. Only diethyl adipate was detected. The MS analysis of the reaction mixture matched the published spectrum of diethyl adipate (John Wiley & Sons, Inc.; Spectrum ID: ID_WID-DLO-074933-7). An 11% yield of diethyl adipate was obtained.

5.11. 2,5-heptanedione (entry 7)

Activated copper (10 mmol) was formed in a reaction vessel after which the temperature of the solution was lowered to -70°C . Ethyl bromide (5 mmol) was syringed into the flask along with the GC internal Standard (decane, 2 mmol). The solution was stirred for 30 min. to produce the organocopper reagent. Then CO was bubbled through the reaction mixture for 0.75 hr. while maintaining the temperature at -70°C . Methyl vinyl ketone (15 mmol) was added and the solution stirred for an additional 2hr. as the temperature was allowed to slowly raise to -40°C . The reaction was quenched with dilute H_2SO_4 . A sample of the reaction mixture was withdrawn, submitted to GC analysis, and compared to an authentic sample of 2,5-heptanedione purchased from the Alfa Chemistry Company. The MS analysis matched that of the published spectrum (John Wiley & Sons, Inc.; Spectrum ID: CAS2009_1_015021). Only a trace (<3% yield) of 2,5-heptanedione was detected.

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Conflict of Interest: The authors declare they have no conflict of interest.

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