

## Remarkably Stable *ortho*-Halophenylcopper Reagents

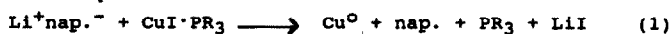
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*Abstract:* We wish to report the generation of remarkably stable *o*-halophenylcopper reagents at room temperature by the direct oxidative addition of activated copper to *o*-fluoro- and *o*-chloriodobenzene. The reagents will undergo substitution reactions with suitable organic halides at 25°C.

Nucleophilic *o*-halometallobenzenes have traditionally been formed by the treatment of halobenzenes with strong base or by oxidative addition of highly reactive metals such as lithium or magnesium to 1,2-dihalobenzenes.<sup>1</sup> At room temperature the resulting organometallics usually undergo a facile 1,2-elimination to produce benzyne and do not have sufficient lifetimes in solution to be viable *o*-halophenyl nucleophiles.<sup>2</sup> Indeed, only at low temperatures, often approaching -100°C, do these organometallics persist in significant quantity.<sup>3,4</sup> At such temperatures these compounds become inconvenient and somewhat difficult to use. Some desired substitution reactions simply proceed too slowly (if at all) at these temperatures. Thus, the development of thermally robust *o*-halophenyl nucleophiles would be very useful for organic synthesis.

Rieke<sup>5</sup> and Ebert<sup>6</sup> have developed a highly reactive form of copper which permits the direct formation of organocopper compounds without utilizing traditional organolithium or Grignard precursors<sup>7</sup>. While variations of the original procedure have been examined<sup>8</sup>, active copper is typically formed by reducing an ethereal solution of CuI·PR<sub>3</sub> with an ethereal solution of lithium naphthalene. The resulting copper is sufficiently reactive to allow a very facile direct oxidative addition to alkyl and aryl halides (eqs 1 and 2).



The high reactivity of this copper led us to believe that it would be feasible to produce *o*-halophenylcopper reagents at room temperature. Upon applying this reaction to *o*-haliodobenzenes we were very pleased to find that, with the exception of *o*-bromiodobenzene, the respective *o*-halophenylcopper reagents could be easily prepared at 25°C as illustrated in Table I.

TABLE I. Formation of *o*-Halophenylcopper Reagents (2)  
From 2-Haloiodobenzenes (1) and Activated Copper<sup>a</sup>

$$\begin{array}{c}
 \text{o-XC}_6\text{H}_4\text{I} \xrightarrow{\text{Cu}^0} [\text{o-XC}_6\text{H}_4\text{Cu}] \xrightarrow{\text{H}^+} \text{XC}_6\text{H}_5 \\
 \text{1} \qquad \qquad \qquad \text{2} \qquad \qquad \qquad \text{3}
 \end{array}$$

compound	X	temperature	% yield <sup>b</sup> of 3
1a	F	25°C	76%
1b	Cl	25°C	74%
1c	Br	-78°C	18% <sup>c</sup>

<sup>a</sup>All reactions were run under argon in TEF or DME. The Cu<sup>0</sup>/*o*-XC<sub>6</sub>H<sub>4</sub>I ratio was 2/1 and the active copper was derived from the reduction of CuI·P(St)<sub>3</sub>. Reactions were found to be complete within 10 min. <sup>b</sup>Quantitation was by GC. The yield of 3 found after quenching the reaction was assumed to be indicative of the amount of organocopper (2) present at the time of the quench. <sup>c</sup>Yields varied from 5% to 34% with a typical value of 18%.





In contrast, yields of *o*-bromophenylcopper (1c) were poor and difficult to reproduce ranging from 5% at room temperature to 34% at -78°C with a typical value of 18%. Since the starting material was completely consumed and the reaction was found to be exothermic, it seems probable that the organocopper reagent is initially formed and then undergoes elimination to produce benzyne and cuprous bromide. The analogous reaction with magnesium or lithium is thoroughly documented.<sup>3c</sup> The stronger carbon-halogen bonds in *o*-chloro- and *o*-fluorophenylcopper apparently raise the activation energy to the extent that the elimination reaction is prevented for these compounds.

The *o*-halophenylcopper intermediates cross-couple with alkyl halides and with acyl chlorides to form the corresponding *o*-haloarenes and *o*-haloketones as shown in Table II. Yields are good except for reactions with *o*-bromophenylcopper (4i, 4j). Repeated attempts failed to couple more than 26% of the brominated organocopper intermediate.

The ability to produce *o*-halophenylcopper reagents opens the door to new synthetic routes for a variety of important and interesting compounds having commercial and biochemical applications as depicted at the bottom of Table II. Intermediate 2a will cross-couple with 2-thiophenecarbonyl chloride to produce 2-*o*-fluorobenzoylthiophene (4k) in an 87% yield. This compound has been used as a replacement for tienilic acid in the development of an assay for 5-hydroxylation reactions by rat liver microsomes.<sup>9</sup> Reagent 2b reacts with 2,4,6-trimethylbenzoyl chloride to form 2'-chloro-2,4,6-trimethylbenzophenone (4l) in an 88% yield. This product is part of a mixture used in thermal recording materials and is utilized in thermal printing.<sup>10</sup>

In conclusion, a practical new method for generating *o*-halophenyl nucleophiles has been established.<sup>11</sup> *o*-Fluoro- and *o*-chlorophenylcopper reagents can be produced in good yields directly from active copper and the respective *o*-haliodobenzenes at 25°C without serious loss due to competing elimination. The organocopper compounds can be utilized in substitution reactions to produce good yields of the *o*-halogenated cross-coupled products. The reactions take place at temperatures which are substantially above the low temperatures required by the analogous lithium or magnesium reagents and thus offer a significant advantage when higher temperatures are needed to effect reaction.

TABLE II. Cross-Coupling Reactions of 2-Halophenylcopper Reagents<sup>a</sup>

$\begin{array}{ccc} o\text{-XC}_6\text{H}_4\text{Cu} & + & \text{RX}' & \longrightarrow & o\text{-XC}_6\text{H}_4\text{R} \\ \text{2} & & & & \text{4} \end{array}$					
compound	X	RX'	no.	product 4	% yield <sup>b</sup> of 4
2a	F	CH <sub>3</sub> I	4a	<i>o</i> -FC <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	100 (76)
2a	F	PhCH <sub>2</sub> Br	4b	<i>o</i> -FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Ph	90 (65)
2a	F	PhCOCl	4c	<i>o</i> -FC <sub>6</sub> H <sub>4</sub> (CO)Ph	96 (73)
2a	F	CH <sub>3</sub> COCl	4d	<i>o</i> -FC <sub>6</sub> H <sub>4</sub> (CO)CH <sub>3</sub>	75 (57)
2b	Cl	CH <sub>3</sub> I	4e	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	77 (57)
2b	Cl	CH <sub>3</sub> CH <sub>2</sub> I	4f	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH <sub>3</sub>	93 (69)
2b	Cl	PhCOCl	4g	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> (CO)Ph	81 (60)
2b	Cl	CH <sub>3</sub> COCl	4h	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> (CO)CH <sub>3</sub>	88 (65)
2c	Br	CH <sub>3</sub> I	4i	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	26 (5)
2c	Br	PhCOCl	4j	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub> (CO)Ph	24 (4)
2a	F	 COCl	4k	<i>o</i> -FC <sub>6</sub> H <sub>4</sub> (CO)- 	87 (53)
2b	Cl	 COCl	4l	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> (CO)- 	88 (56)

<sup>a</sup>All reactions were run under argon for 30 min. in THF or DME with a threefold excess of RX'. Reactions with 2a or 2b were performed at 25°C. Reactions of 2c were carried out at -78°C for 30 min. and then allowed to slowly warm to room temperature. <sup>b</sup>Quantitation was by GC. The first value represents the yield based upon the amount of organocopper (2) present just prior to the addition of RX'. The second value (in parentheses) represents the overall yield from starting material.

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## References and Notes

- In this work we will not be considering the formation of pentahalometallobenzenes which are rather easily obtained or the formation of non-nucleophilic compounds such as organomercury reagents.
- For reviews discussing formation of nucleophilic o-halometallobenzenes and their subsequent elimination to produce o-benzyne see the following papers and the references cited therein: (a) Bryce, M. R.; Vernon, J. M. *Advances in Heterocyclic Chemistry* 1981, 28, 183. (b) Wittig, G. *Angew. Chem. Internat. Edit.* 1965, 4, 731. (c) Heaney, H. *Chemical Reviews* 1962, 62, 81. (d) Bunnett, J. F. *J. Chem. Ed.* 1961, 38, 278.
- (a) Iwao, M. *J. Org. Chem.* 1990, 55, 3622. (b) Heaney, H.; Mann, F. G.; Millar, I. T. *J. Chem. Soc.* 1956, 4692. (c) Gilman, H.; Gorsich, R. D.; *J. Am. Chem. Soc.* 1956, 78, 2217.
- o-Haloarylcopper reagents have been previously reported in the literature and are usually formed by low temperature transmetalation of the corresponding o-haloaryl lithium compound. Recent examples include: (a) Lipshutz, H.B.; Seigmann, K.; Garcia, E. *J. Am. Chem. Soc.* 1991, 113, 8161. (b) Widdowson, D.A.; Beswick, P.J. *Synthesis* 1985, 492.
- (a) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* 1984, 49, 5280. (b) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* 1988, 53, 4482. (c) Rieke, R. D.; Wehmeyer, R. M.; Wu, T. -C.; Ebert, G. W. *Tetrahedron* 1989, 45, 443.
- Ginah, F. O.; Donovan, T. A. Jr.; Suchan, S. D.; Pfennig, D. R.; Ebert, G. W. *J. Org. Chem.* 1990, 55, 584. (b) Ebert, G. W.; Klein, W. R. *J. Org. Chem.* 1991, 56, 4744. (c) Ebert, G. W.; Cheasty, J. W.; Tehrani, S. S.; Acouad, E. *Organometallics* 1992, 11, 1560.
- For reviews on the direct syntheses of organometallic compounds see the following papers and the references cited therein: (a) Rieke, R. D. *Science* 1989, 246, 1260. (b) Massey, A. G.; Humphries, R. E. *Aldrichimica Acta* 1989, 22(2), 31. (c) Davis, S. C.; Klambunde, K. *J. Chem. Rev.* 1982, 82, 153. (d) Rochow, E. G. *J. Chem. Ed.* 1966, 43, 58.
- (a) Stack, D. E.; Dawson, B. T.; Rieke, R. D. *J. Am. Chem. Soc.* 1991, 113, 4672. (b) Wu, T. -C.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* 1987, 52, 5057. (c) Wehmeyer, R. M.; Rieke, R. D. *Tetrahedron Lett.* 1988, 29, 4513. (d) Rieke, R. D.; Wu, T. -C.; Stinn, D. E.; Wehmeyer, R. M. *Synth. Commun.* 1989, 19, 1833.
- Neau, E.; Dansette, P. M.; Andronik, V.; Mansuy, D. *Biochem. Pharmacol.* 1990, 39, 1101.
- Satomura, M.; Iwakura, K.; Igarashi, A. *Jpn. Kokai Tokkyo Koho* 1987, 5 pp.
- The basic experimental procedure for preparing activated copper has been previously reported.<sup>6a,c</sup> In a typical reaction, active copper (10 mmol) was produced by the lithium naphthalenide reduction of  $\text{CuI}\cdot\text{P}(\text{Et})_3$  in THF or DME. The temperature of the reaction was adjusted and o-haliodobenzene (1) was added (5.0 mmol) along with the internal standard (typically decane, 2 mmol). The solution was stirred for 10 min. to achieve the maximum yield of organocopper (2). To cross-couple, three equivalents (15 mmol) of organic halide substrate ( $\text{RX}^1$ ) was injected, neat, into the reaction mixture and allowed to stir for 30 min. The products were characterized and identified by their spectral and physical properties after employing standard workup and isolation procedures as previously published.<sup>6a,c</sup> All products synthesized in this work have been previously reported in the literature and most are commercially available. Quantitation was by GC using the internal standard method.