

Preparation of Functionalized Zinc and Copper Organometallics Containing Sulfur Functionalities at the Alpha or Gamma Position

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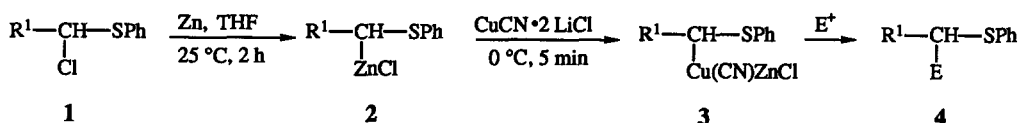
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Summary: α -Chloroalkyl phenyl sulfides **1** readily insert zinc in THF at 25 °C (0.5-2 h), affording sulfur stabilized organozinc derivatives of type **2**. The presence of a functional group such as an ester or a cyano group is tolerated in these organometallics. After a transmetalation to the corresponding copper reagent **3**, they react with a wide range of electrophiles. Zinc and copper organometallics bearing a thiophenyl or a phenylsulfanyl group at the γ -position have also been prepared showing the generality of our approach.

Organolithiums stabilized by sulfur¹ are important carbanionic intermediates in organic synthesis. Their excellent ability to form new carbon-carbon bonds combined with the easy conversion of the sulfur group to various other functionalities has led to numerous synthetic applications. However, the high reactivity of these reagents prohibits the presence of most functional groups in these organometallics. Herein, we report a new approach to α -thiocarbanions of zinc and copper allowing for the first time the presence of functional groups such as an ester- or a cyano-group in these compounds.

We have recently found that the presence of an oxygen at the alpha position to a carbon-halide bond considerably facilitates the insertion of zinc into this carbon-halide bond, affording organozinc halides at the alpha position to oxygen.² We have

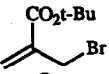
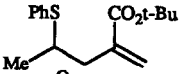
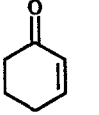
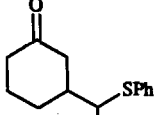
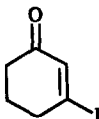
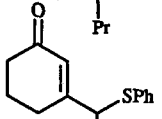
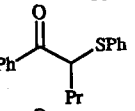
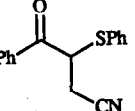
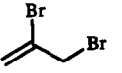
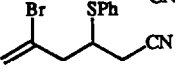
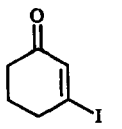
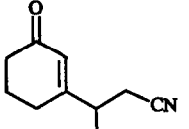
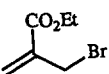
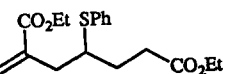
Scheme I



now observed that a sulfur atom exerts a similar effect and allows a very fast insertion of zinc into an adjacent carbon-chlorine bond. Thus, the treatment of an α -chloroalkyl phenyl sulfide^{3,4} **1** with zinc dust⁵ in THF at 25 °C for 2 h furnishes the corresponding organozinc chloride⁶ **2** in excellent yields (> 85%). The addition of CuCN · 2 LiCl⁵ converts **2** to the copper organometallic **3** which reacts with typical organic electrophiles^{7,8} leading to polyfunctional thioethers of type **4** (Table I and Scheme I).⁹ The coupling of **3a** with an alkynyl bromide^{7d} gives the expected propargylic thioether **4a** in 70% yield (1-bromooctyne (0.75 eq.), THF, -60 °C, 12 h; entry 1). The addition of **3a** to benzaldehyde (0.5 eq.) in the presence of BF₃ · OEt₂ (2 eq.) affords the alcohol **4b** in 71% yield (-78 °C to -20 °C, 2 h; entry 2). Allylations of the substituted copper derivatives **3b**, **3d**, and **3e** proceed readily and in good yields (75-92%; allylic bromide (0.8 eq.), -40 °C to 0 °C, 0.5 h; entries 3, 8 and 10). The Michael addition of **3c** to 2-cyclohexenone⁵ (0.63 eq.) produces the desired 1,4-adduct **4d** (Me₃SiCl (2 eq.), THF, -78 °C to 25 °C, overnight; 78%; entry 4). The addition-elimination of **3c** and of the cyano-substituted organocopper **3d** to 3-iodocyclohexenone¹⁰ gives the cyclohexenones **4e** and **4i** in 88% and 86% yields respectively (-78 °C to -20 °C, 12 h, entries 5 and 9). Finally, the benzylation of **3c** and **3d** affords the α -thiophenyl ketones **4f** (93%) and **4g** (79%) under mild reaction conditions (PhCOCl (0.62 eq.), THF, -10 °C, 12 h; entries 6 and 7).

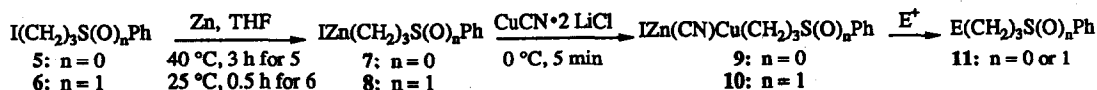
Whereas β -sulfur-substituted zinc organometallics could not be prepared,¹¹ certainly because of their high propensity to undergo a β -elimination, the preparation of the γ -thiophenyl and γ -phenylsulfinyl zinc reagents respectively **7** and **8** from the corresponding iodides **5** and **6** proceeds smoothly and in excellent yields (> 85%). It should be mentioned that the polar sulfoxide group at the gamma position considerably facilitates the preparation of **8** (zinc dust (2.5 eq.), THF, 25 °C, 0.5 h) compared to the γ -thiophenyl-substituted derivative **7** (zinc dust (2.5 eq.), THF, 40 °C, 3 h). The addition of CuCN·2 LiCl

Table I. Products of Type 4 Obtained by the Reaction of the (α -Thioalkyl) Zinc and Copper Organometallics **3** with Organic Electrophiles.¹³

Entry	Organometallic 3	Electrophile	Product of Type 4	Yield (%)
1	PhSCH ₂ Cu(CN)ZnCl	3a 1-bromooctyne	PhSCH ₂ —Hex	4a 70
2	3a	PhCHO	PhSCH ₂ CH(OH)Ph	4b 71
3	PhSCH(CH ₃)Cu(CN)ZnCl	3b 		4c 87
4	PhSCH(Pr)Cu(CN)ZnCl	3c 		4d 78 ^a
5	3c			4e 88
6	3c	PhCOCl		4f 93
7	PhSCH(CH ₂ CN)Cu(CN)ZnCl	3d PhCOCl		4g 79
8	3d			4h 75
9	3d			4i 86
10	PhSCH((CH ₂) ₂ CO ₂ Et)Cu(CN)ZnCl 3e			4j 92

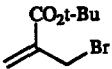
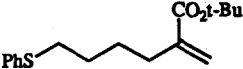
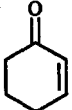
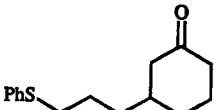
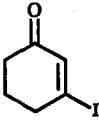
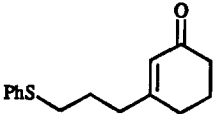
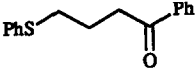
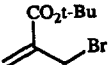
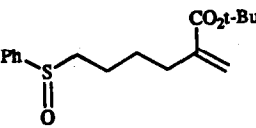
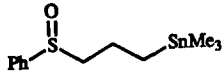
^a Product **4d** is obtained as a 1:1 mixture of diastereoisomers

Scheme II



leads to the copper reagents **9** and **10** which react readily with various electrophiles (Scheme II and Table II). The allylation of **9** and **10** with tert-butyl α -(bromomethyl)acrylate¹² (entries 1 and 5 of Table II) furnishes the sulfur-substituted unsaturated esters **11a** (87%) and **11e** (85%). The Michael addition of **9** to 2-cyclohexenone (0.75 eq.) gives, in the presence of chlorotrimethylsilane (2 eq.), the 3-substituted cyclohexanone **11b** in 84% yield (-78 °C to 25 °C, overnight; entry 2). The reaction of **9** with 3-iodocyclohexenone¹⁰ (0.75 eq.); -78 °C to -25 °C, 15 h) gives the substitution product **11c** in 85% yield (entry 3). The benzoylation of **9** leads to the ketone **11d** (PhCOCl (0.75 eq., -10 °C, 10 h; 80% yield; entry 4). The stannylation of **10** with trimethyltin chloride (0.62 eq.) gives the stannylated sulfoxide **11f** in excellent yield (THF, -20 °C to 25 °C, 0.5 h; 90%; entry 6).

Table II. Products of Type 11 Obtained by the Reaction of the Copper Reagents **9** and **10** with Organic Electrophiles.¹³

Entry	Copper Reagent	Electrophile	Product of Type 11	Yield (%) ^a
1	PhS(CH ₂) ₃ Cu(CN)ZnI 9			87
2	9			84
3	9			85
4	9	PhCOCl		80
5	PhS(O)(CH ₂) ₃ Cu(CN)ZnI 10			85
6	10	Me ₃ SnCl		90

In summary, we have developed a new approach to α -thioorganometallics of zinc and copper which for the first time can bear functional groups. This should considerably extend the synthetic potential of α -thiocarbanions. Further new organometallic reagents of zinc and copper bearing sulfur functionalities such as thioesters, sulfones are currently being studied in our laboratories and will be reported in due course.

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- The copper reagents **3** were found to be less reactive than RCu(CN)ZnI (R = alkyl, prim. or sec.) and no reaction was observed with diethyl benzylidenemalonate or nitrostyrene.
- Typical procedure: (a) Preparation of 2-cyano-1-phenylthioethylzinc chloride **2d**. A 50 mL, three-necked flask equipped with a dropping funnel, a thermometer and an argon inlet was charged with zinc dust (Aldrich, -325 mesh, 1.95 g, 30 mmol) in 2 mL of THF. After zinc activation with dibromoethane (ca. 300 mg; see ref. 5), a solution of 3-chloro-3-phenylthiopropionitrile (1.98 g, 10 mmol) in 6 mL of THF was added at 25 °C. After 2 h at 25 °C, GLC analysis of a hydrolyzed aliquot showed no chloride remaining. The reaction mixture was allowed to settle.
(b) Reaction of **2d** with 3-iodocyclohexenone:¹⁰ preparation of 3-(2-cyano-1-phenylthioethyl)cyclohexenone **4i** (entry 9 of Table I). The supernatant solution of the organozinc chloride prepared above was transferred via syringe to a solution of dry LiCl (dried for 1 h at 120 °C at 0.1 mmHg; 0.68 g; 16 mmol) and CuCN (0.72 g, 8 mmol) in 6 mL of THF at -40 °C. The resulting greenish suspension was warmed to 0 °C and stirred for 5 min. After cooling to -70 °C, a solution of 3-iodocyclohexenone (1.11 g, 5 mmol) in 2 mL of THF was added and the reaction was allowed to warm to 0 °C and was stirred at this temperature for 12 h. After a standard workup procedure, the residue obtained after evaporation of the solvents was purified by flash chromatography (solvent: 1:3 ratio of ethyl acetate and hexane) providing 1.1 g (86% yield) of the analytically pure cyclohexenone derivative **4i**.
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- All yields refer to isolated yields of analytically pure products. Satisfactory spectral data (IR, ¹H and ¹³C NMR, mass spectra, high resolution mass spectra) has been obtained for all compounds.