

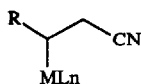
Synthesis and Reactivity of Open-Chain and Cyclic 2-Cyano Zinc and Copper Organometallics

Tahir N. Majid, Ming Chang P. Yeh and Paul Knochel*

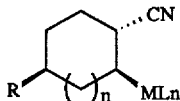
Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

Summary: Various open-chain and cyclic β -cyano zinc and copper organometallics can be prepared by the reaction of the corresponding organic halides with zinc and subsequent transmetalation with $\text{CuCN} \cdot 2 \text{LiCl}$. They react in fair to good yields with various organic electrophiles (enones, allylic bromides and benzoyl chloride) affording highly functionalized nitriles. High diastereoselectivities have been observed in coupling reactions with the cyclic 2-cyano organocopper derivatives. The x-ray structure of cyanoethylzinc iodide is also reported.

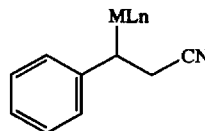
The copper organometallics $\text{RCu}(\text{CN})\text{ZnI}$, prepared from the corresponding organozinc compounds RZnI by addition of the soluble copper salt $\text{CuCN} \cdot 2 \text{LiCl}$, are versatile reagents which display a good reactivity toward various electrophiles such as enones, acid chlorides, allylic halides, 1-haloalkynes and acetylenic esters.¹ The preparation of *highly functionalized* reagents $\text{RCu}(\text{CN})\text{ZnI}$ is of special interest and we have previously reported the first synthesis of the 2-cyano organozinc and copper reagents **1a** and **1b**.² We have now found that more substituted compounds of this type such as **2**, **3**, **4**, **5**, and **6** ($\text{MLn} = \text{ZnX}$ or $\text{Cu}(\text{CN})\text{ZnX}$) can be readily prepared and that they can act as efficient d^3 reagents.³ The zinc organometallics **2a-6a** were obtained from the corresponding iodides or chloride⁴ (for **6a**) and zinc (cut foil or dust) in THF (or in THF:



1a: R = H; $\text{MLn} = \text{ZnI}$
1b: R = H; $\text{MLn} = \text{Cu}(\text{CN})\text{ZnI}$
2a: R = Pr; $\text{MLn} = \text{ZnI}$
2b: R = Pr; $\text{MLn} = \text{Cu}(\text{CN})\text{ZnI}$



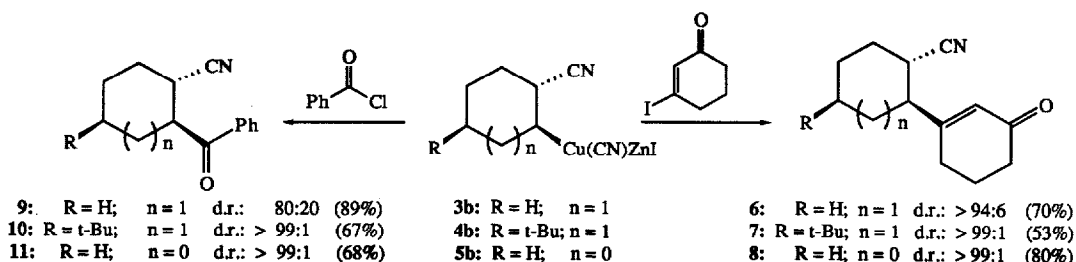
3a: R = H; n = 1; $\text{MLn} = \text{ZnI}$
3b: R = H; n = 1; $\text{MLn} = \text{Cu}(\text{CN})\text{ZnI}$
4a: R = t-Bu; n = 1; $\text{MLn} = \text{ZnI}$
4b: R = t-Bu; n = 1; $\text{MLn} = \text{Cu}(\text{CN})\text{ZnI}$
5a: R = H; n = 0; $\text{MLn} = \text{ZnI}$
5b: R = H; n = 0; $\text{MLn} = \text{Cu}(\text{CN})\text{ZnI}$



6a: $\text{MLn} = \text{ZnCl}$
6b: $\text{MLn} = \text{Cu}(\text{CN})\text{ZnCl}$

DMSO (9:1) in the case of **6a**)⁵ at temperatures between 5° C and 30° C. After 3-5 h, the reaction was complete as judged by GLC analysis of hydrolyzed aliquots (80-90% yield).⁶ Remarkably, these organozincs show no significant tendency to eliminate X-Zn-CN . For example, the preparation of **6a**, which requires a temperature of 30° C and a relatively polar solvent (THF/DMSO), gives less than 6-8% of styrene as elimination product. The reagents **2b-6b**, obtained by the addition of $\text{CuCN} \cdot 2 \text{LiCl}$ (1 eq., 0° C, 5 min.) to **2a-6a**, react in fair to excellent yields with benzoyl chloride (0° C, 2 h; see Table I entries 1 and 11), 3-iodocyclohexenone⁷ (-30° C, 10-20 h; see entries 2 and 13), enones (-78° C to 25° C, overnight; see entries 3-5, 7 and 9) and allylic bromides (0° C, 2 h; see entries 6, 8, 10, and 12). Compared to other functionalized $\text{RCu}(\text{CN})\text{ZnI}$ reagents, these 2-cyano substituted organometallics show a somewhat lower reactivity and do not react efficiently with 1-haloalkynes, nitro-olefins or acetylenic esters.^{1d} High diastereoselectivities were observed in the reaction of the cyclic copper compounds **3b**, **4b**, and **5b** with electrophiles (see Table I and Scheme 1), especially with 3-iodocyclohexenone which affords almost exclusively the *trans* cyanoenones **6** (d.r. (diastereoisomeric ratio) >94:6; 70% yield, $^3J_{\text{trans}} = 11.7 \text{ Hz}$), **7** (d.r. >99:1; 53% yield), and **8** (d.r. >99:1; 80% yield).⁸ Benzoyl chloride and allylic bromides give less selective reactions leading generally to 1:4 *cis-trans* ratios (see Table I and Scheme 1). However, the t-butyl substituted copper organometallic **4b** and the

Scheme I



2-cyano-cyclopentyl copper derivative **5b** furnish with benzoyl chloride only the trans-substituted products **10** (67%) and **11** (68%) respectively. The stereochemistry of these coupling products does not depend on the stereochemistry of the starting iodides. We observed that pure cis-1-cyano-2-iodocyclohexane rapidly isomerizes to a 60:40 ratio of trans:cis isomers during the formation of the zinc reagent **3a**. The iodolysis of **3a** (I_2 (1.2 eq.), -78°C , 10 min.) affords a 88:12 ratio of trans- and cis-1-cyano-2-iodocyclohexane suggesting the same ratio for the zinc compound **3a**. The higher d.r. observed in the reactions with benzoyl chloride or 3-iodocyclohexenone may be explained by the faster reaction of the trans-organocopper derivative with these electrophiles.

In order to understand the stability of β -cyano organometallics, 2-cyanoethylzinc iodide was crystallized in THF and its x-ray structure⁹ was determined. It was found that the zinc atom coordinates one molecule of THF and the cyano group of another molecule forming polymeric chains in the crystal (see Figure 1). Noteworthy is the almost perfect antiperiplanar arrangement between the C–ZnI bond and the C–CN bond and the relatively long bond length of C–CN (1.50 Å compared to a usual value of 1.44 ± 0.01 Å), indicating the elimination tendency of the cyano group. Further studies concerning the reactivity and the diastereoselectivity of β -cyano organometallics are currently underway in our laboratories.

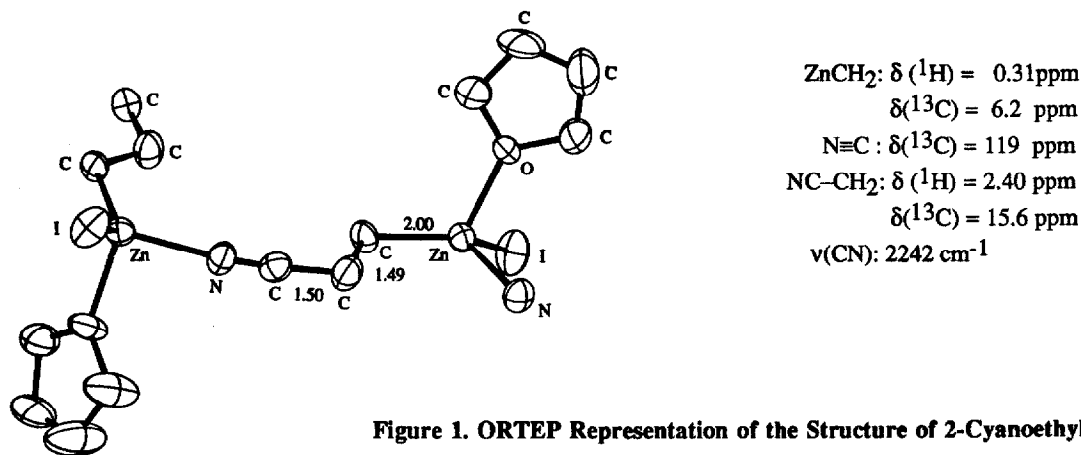


Figure 1. ORTEP Representation of the Structure of 2-Cyanoethylzinc Iodide Determined by X-ray Analysis and Significant Analytical Data

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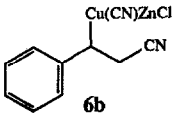

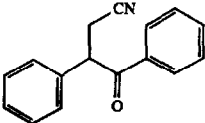
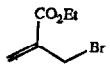
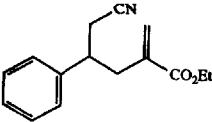
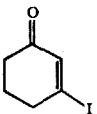
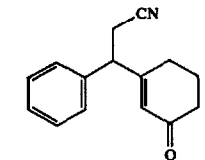
References and Notes

- (a) Knochel, P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390; (b) Yeh, M.C.P.; Knochel, P.; Santa, L.E. *Tetrahedron Lett.* **1988**, *29*, 3887; (c) Yeh, M.C.P.; Knochel, P.; Butler, W.M.; Berk, S.C. *Tetrahedron Lett.* **1988**, *29*, 6693; (d) Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* **1989**, submitted for publication.

Table I. Polyfunctional Nitriles Obtained by the Reaction of the Copper Reagents **2b-6b** with Enones, Allylic Bromides and an Acid Chloride.

Entry	Copper Reagent	Electrophile	Product	Diastereomeric Ratio	Yield (%) ^a
1		PhCOCl		—	81
2	2b			—	88
3	2b			67:33	84
4	2b			76:24	83
5	3b			21:45:34	76
6	3b			82:18	95
7	3b			83:17 ^b	62
8	3b			80:20	87
9	4b			50:50 (at C-3) ^b	86
10	5b			86:14	86

Table I. (cont'd)

Entry	Copper Reagent	Electrophile	Product	Diastereomeric Ratio	Yield (%) ^a
11				-	82
12	6b			-	82
13	6b			-	89

^a All indicated yields are isolated yields of analytically pure compounds. Satisfactory spectral data (IR, ¹H and ¹³C-NMR, high resolution mass spectra) were obtained for all compounds.

^b Only two diastereoisomers are formed as indicated by the ¹³C-NMR spectra and by capillary GLC analysis.

References and Notes

- (a) Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395; (b) During the preparation of this manuscript, the synthesis of some cyano-substituted organozinc compounds have been reported: Tamaru, Y.; Tanigawa, H.; Yamamoto, T.; Yoshida, Z. *Angew. Chem.* **1989**, *101*, 358; *ibid.*, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 351.
- Seebach, D. *Angew. Chem.* **1979**, *91*, 259; *ibid.*, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.
- (a) 3-Iodohexanenitrile was prepared in two steps: (i) addition of butyraldehyde to lithioacetonitrile, 66% yield, (Kaiser, E.M.; Hauser, C.R. *J. Org. Chem.* **1968**, *33*, 3402); (ii) iodination with PPh₃, I₂ and imidazole at 25° C, 56% yield (Corey, E.J.; Wess, G.; Xiang, Y.B.; Singh, A.K. *J. Am. Chem. Soc.* **1987**, *109*, 4717).
- (b) 1-cyano-2-iodocyclohexane was prepared by the addition of NaI (3 eq.), Me₃SiCl (3 eq.) and H₂O (1.5 eq.) to 1-cyanocyclohexene; 81% yield (Irfune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1988**, 366).
- 4-t-Butyl-1-cyano-2-iodocyclohexane and 1-cyano-2-iodocyclopentane were prepared in a similar way.
- (c) 2-chloro-2-phenylpropionitrile was prepared in two steps: (i) addition of benzaldehyde to lithioacetonitrile (64% yield); (ii) chlorination with SOCl₂ (12 eq.; benzene, 5° C, 3 h; 47% yield).
- Zakharkin, L.I.; Ikhlobystin, O.Y. *Izv. Akad. SSSR* **1963**, *193*; *C.A.* **1963**, *58*, 12589a; Berk, S.C.; Yeh, M.C.P.; Jeong, N.; Knochel, P. manuscript in preparation.
- Typical Procedure:
 - Preparation of 2-cyano-1-cyclohexylzinc iodide. A THF solution of 1.50 g (6.4 mmol in 3 mL of THF) of 2-cyano-1-iodocyclohexane was added dropwise to 1 g (15 mmol) of activated¹ cut zinc foil at 5° C. After 3.5 h at this temperature, the formation of the zinc derivative **3a** was complete as judged by GLC analysis (100 mg of decane was added as an internal standard). A yield of 80-90% of **3a** was obtained.
 - Reaction with ethyl bromomethylacrylate. The reagent **3a** was transferred to a solution of 0.56 g (6.4 mmol) of CuCN and 0.54 g (12.8 mmol) of LiCl in 6 mL of THF at -20° C. The resulting creamy yellow solution was stirred for 10 min. at 0° C before cooling to -70° C and adding 0.77 g (4 mmol) of ethyl bromomethylacrylate in 2 mL of THF. After 1 h at 0° C, the reaction mixture was worked up as usual. Purification of the oily residue by flash chromatography (solvent: hexane/AcOEt 20:1) yielded 840 mg (95%) of ethyl 2-(2-cyanocyclohexylmethyl) acrylate (see entry 6 of Table I) as a cis/trans mixture of 18:82. The ¹H-NMR spectrum shows for the major isomer (trans isomer): δ (H-α(CN)): 2.80-2.86 ppm, dd, ³J_{ax-ax} = 13.7 Hz, ³J_{eq-ax} = 2.8 Hz. The minor isomer (cis isomer) shows a broad doublet for this proton.
- Piers, E.; Nagakura, I. *Synth. Comm.* **1975**, *5*, 193.
- The trans configuration of **8** was assigned from NOE experiments: irradiation of the α-CN proton gave no enhancement of the 5-membered ring allylic proton, whereas a 7% enhancement of the vinylic proton (α to carbonyl) was observed. Irradiation of the 5-membered ring allylic proton gave no enhancement of the α-CN proton.
- Crystallographic data for 2-cyanoethylzinc iodide crystal system: monoclinic; group space: P2₁/m [a = 8.650(2) Å, b = 9.854 (3); c = 12.846 (4), β = 97.44 (2)] d calc. = 1.948 g/cm³; λ (MoKα) = 0.71069 Å; V = 1085.7 (6) Å³; Z = 4; crystal size (mm): 0.290 x 0.303 x 0.634; no. unique data > 2σ (I): 1137; R = 0.063; R_w = 0.060.