

The Reactivity of the Highly Functionalized Copper, Zinc Reagents
RCu(CN)ZnI Toward 1-Haloalkynes and Acetylenic Esters

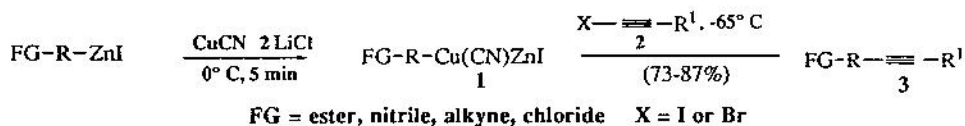
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Summary: The highly functionalized organometallics RCu(CN)ZnI **1** react efficiently with 1-haloalkynes providing polyfunctionalized alkynes in high yields. This method has been used to prepare a pheromone of the *Amathes c-nigrum* in 3 steps and 64% overall yield. The reagents **1** also add in the presence of an excess of Me₃SiCl to acetylenic esters to afford polyfunctionalized C-silylated ethylenic esters. In the case of ethyl propiolate, the reaction is highly stereoselective and affords 97% pure (E)-2-trimethylsilyl ethylenic esters.

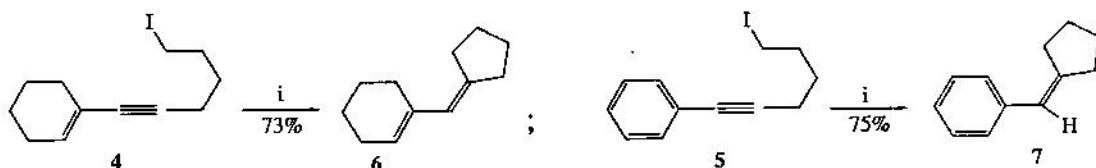
The high covalent character of the carbon-zinc bond allows the synthesis of highly functionalized organozinc compounds RZnX^{1,2} which can be converted to the corresponding copper derivatives RCu(CN)ZnX **1** by the addition of the soluble copper salt CuCN · 2 LiCl.² These copper reagents react efficiently with various electrophiles such as enones, allylic halides, acyl chlorides and aldehydes.² We now report that the polyfunctional copper compounds **1** react under very mild conditions with 1-bromo- and 1-iodo-alkynes^{3,4} **2a-d** affording the highly functionalized alkynes **3a-3j** in good yields⁵ (73-87%; see Scheme I and Table I). The best results are obtained by performing the reactions at low temperature

Scheme I







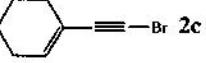

(-78° C to -55° C) in order to avoid halogen-metal exchange reactions, especially in the case of 1-iodooctyne **2b**. Under these conditions, reaction times of 16-18 hr. are usually required for the haloalkynes **2a-2c**. Noteworthy is the case of 1-bromo-2-phenylacetylene **2d** which affords the coupling products after much shorter reaction times (1-4 hr. at -78° C), indicating that the mechanism of the reaction may be an addition-elimination reaction involving a rate determining syn carbocupration⁶ followed by an anti-elimination. Two of the polyfunctional alkynes produced (**3f;3j**) were converted to the corresponding iodides **4** and **5** in 82% and 79% yield respectively (NaI, acetone, 16 hr. reflux). Their reaction with zinc (2.5 equiv.) in THF (40° C, 1 hr., then 23° C, 16 hr.) furnishes, after hydrolysis, the cyclized olefins **6** and **7** in 73% and 75% yield respectively;⁷(see Scheme II). We have applied this methodology in a very short synthesis of the pheromone of the *Amathes c-nigrum* **8**.⁸ Thus the treatment of oxepane (0.4 mol) and NaI (0.5 mol) at 0° C in acetonitrile with acetyl

Scheme II



i: Zn (2.5 eq.), THF, 40° C, 1 hr, then 16 hr at 23° C

Table I. Alkynes 3a-3j Obtained by the Reaction of RCu(CN)ZnI **1** with the 1-Haloalkynes 2a-2d.

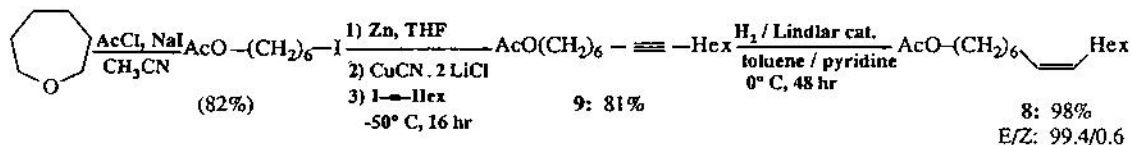
Entry	RCu(CN)ZnI	1-Haloalkyne	Products 3	Yield (%) ^a
1	NC-(CH ₂) ₃ -Cu(CN)ZnI	Br≡-Hex 2a	NC-(CH ₂) ₃ -≡-Hex 3a	81
2	EtO ₂ C-(CH ₂) ₃ -Cu(CN)ZnI	Br≡-Hex 2a	EtO ₂ C-(CH ₂) ₃ -≡-Hex 3b	78
3	c-HexCu(CN)ZnI	Br≡-Hex 2a	c-Hex≡-Hex 3c	87
4	CH ₃ -CH(OPiv)-(CH ₂) ₃ -Cu(CN)ZnI	I≡-Hex 2b	CH ₃ -CH(OPiv)-(CH ₂) ₃ -≡-Hex 3d	75
5	NC-(CH ₂) ₃ -Cu(CN)ZnI	 2c	NC-(CH ₂) ₃ -≡-  3e	79
6	Cl-(CH ₂) ₄ -Cu(CN)ZnI	 2c	Cl-(CH ₂) ₄ -≡-  3f	81
7	EtO ₂ C-(CH ₂) ₃ -Cu(CN)ZnI	 2c	EtO ₂ C-(CH ₂) ₃ -≡-  3g	74
8	Pent≡-(CH ₂) ₃ -Cu(CN)ZnI	Ph≡-Br 2d	Pent≡-(CH ₂) ₃ -≡-Ph 3h	86
9	EtO ₂ C-(CH ₂) ₃ -Cu(CN)ZnI	Ph≡-Br 2d	EtO ₂ C-(CH ₂) ₃ -≡-Ph 3i	73
10	Cl-(CH ₂) ₄ -Cu(CN)ZnI	Ph≡-Br 2d	Cl-(CH ₂) ₄ -≡-Ph 3j	71

^a Isolated yields of analytically pure products. Satisfactory spectral data (IR, ¹H and ¹³C-NMR, High resolution mass spectra) were obtained for all new compounds.

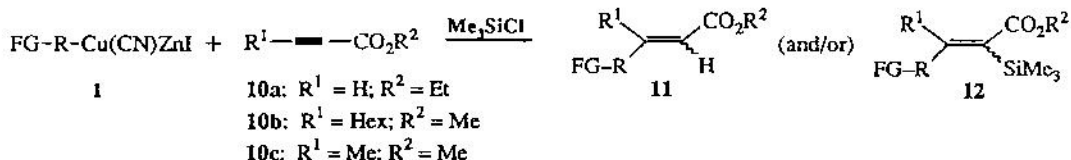
chloride (0.5 mol) affords, after distillation, 1-acetoxy-6-iodohexane in 82% yield.⁹ This iodide was converted into 6-acetoxyhexylzinc iodide (3 eq. of zinc activated with dibromoethane,^{2a} 40° C, 10 hr.) in over 95% yield. Formation of the corresponding copper derivatives (CuCN · 2 LiCl, 0° C, 5 min.) and coupling with 1-iodooctyne (0.77 eq., -78° C, then 16 hr. at -50° C) affords 7-tetradecyn-1-yl acetate **9** in 81% isolated yield (10 mmol scale experiment). Lindlar hydrogenation (H₂, 1 atm, Pd/CaCO₃/PbO; toluene/pyridine= 6/1, 0° C, 48 hr) of **9** gives the desired pheromone **8** with over 99.4% in 98% yield (> 99.4% Z, see Scheme III).

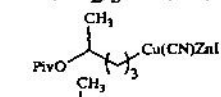
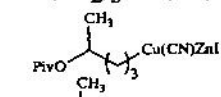
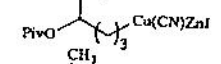
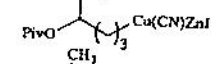
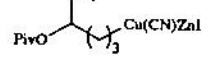
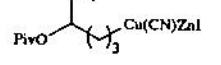
During this study, we also found that the functionalized copper reagents **1** are able to react with acetylenic esters of type **10**¹⁰ under well defined conditions, affording either the ethylenic esters **11**, the C-silylated unsaturated esters **12** or a mixture of both¹¹ (see Scheme IV and Table II). Ethyl propiolate **10a** reacts readily with FG-R-Cu(CN)ZnI **1** (-78° C, 1-14 hr.) to afford the pure (E)- ethylenic esters **11** (see entries 1 and 3 of Table II). In the presence of an excess of Me₃SiCl¹² the (E)-silylated product **12** is obtained exclusively in very high stereoisomeric purity (>97% E) and in excellent yields (see entries 2,4, and 5). In the case of substituted acetylenic esters such as **10b** and **10c**, the presence of Me₃SiCl¹² is required for addition and with methyl tetrolate (**10c**), the formation of silylated products of type **12** usually predominates (a mixture of E and Z stereoisomers is formed; see entries 9-11). The bulkier ester **10b** allows better control

Scheme III



Scheme IV

Table II. Ethylenic Esters **11** and **12** Obtained by the Addition of $\text{RCu}(\text{CN})\text{ZnI}$ **1** to the Acetylenic Esters **10a-c**.

Entry	FG-R-Cu(CN)ZnI	Acetylenic ester	No. of equiv. Me ₃ SiCl added	Products 11 and (or) 12			Ratio 11 : 12	Yield (%) ^a
				R ¹	R ²	FG-R-		
1	NC-(CH ₂) ₃ -Cu(CN)ZnI	10a	0	H	Et	NC-(CH ₂) ₃ -	100:0	83 ^b
2	NC-(CH ₂) ₃ -Cu(CN)ZnI	10a	4	H	Et	NC(CH ₂) ₃ -	0:100	84 ^b
3	EtO ₂ C-(CH ₂) ₃ -Cu(CN)ZnI	10a	0	H	Et	EtO ₂ C-(CH ₂) ₃ -	100:0	99 ^b
4	EtO ₂ C-(CH ₂) ₃ -Cu(CN)ZnI	10a	4	H	Et	EtO ₂ C-(CH ₂) ₃ -	0:100	91 ^b
5	Cl-(CH ₂) ₄ -Cu(CN)ZnI	10a	4	H	Et	Cl-(CH ₂) ₄ -	0:100	85 ^b
6	NC-(CH ₂) ₃ -Cu(CN)ZnI	10b	2	Hex	Me	NC-(CH ₂) ₃ -	100:0	82 ^f
7	 -Cu(CN)ZnI	10b	5	Hex	Me	 -	100:0	77 ^{c,f}
8	 -Cu(CN)ZnI	10b	4	Hex	Me	 -	22:78	73 ^{d,f}
9	 -Cu(CN)ZnI	10c	4	Me	Me	 -	12:88	78 ^f
10	AcO-(CH ₂) ₆ -Cu(CN)ZnI	10c	1.6	Me	Me	AcO-(CH ₂) ₆ -	17:81	76 ^{e,f}
11	BuCu(CN)ZnI	10c	4	Me	Me	Bu	9:91	85 ^f

^a Isolated yields of analytically pure products. Satisfactory spectral data (IR, ¹H and ¹³C-NMR, High resolution mass spectra) were obtained for all new compounds. ^b The (E)- isomer was isolated (> 97% stereoisomeric purity). ^c A reaction time of 3 hr at 22° C was used. ^d A reaction time of 18 hr at 22° C was used. ^e The reaction was performed in the presence of two eq. of BF₃ · OEt₂. ^f Obtained as a E/Z mixture of isomers.

of the reaction and affords only the unsilylated product **11** if either short reaction times (3 hr. at 23° C) or a small excess of Me₃SiCl are used.¹³ With longer reaction times (18 hr. at 22° C), the C-silylated ester **12** is again the major product (compare entries 7 and 8). The use of BF₃ · OEt₂ does not improve this selectivity (see entry 10). Further synthetic applications of these and related reactions are currently being studied.

Acknowledgments: We thank the National Institutes of Health (GM 41908) and the Horace H. Rackham School of Graduate Studies of The University of Michigan for the generous support of this work.

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5. Typical procedure: A THF solution of 4-chlorobutylzinc iodide (7 mmol); 1.4 eq. prepared in over 90% from 4-chloro-1-iodobutane²⁴ (40° C, 2 hr. then 23° C, 10 hr.), was added at -10° C to a solution of CuCN · 2 LiCl (7 mmol) in THF (7 ml). After 5 min. at 0° C, the yellow-green solution was cooled to -78° C and 925 mg (5 mmol) of the 1-bromoalkyne **2b** in THF was slowly added. The reaction mixture was stirred 18 hr at -65° C. After the usual work-up and purification by flash chromatography (solvent: hexane), 800 mg of pure **3f** was obtained (81% yield).
6. The easy carbocupration of phenylacetylene is well known; Normant, J.F.; Alexakis, A. *Synthesis* **1981**, 841.
7. Careful monitoring of these reactions did not allow us to detect an intermediate open-chain organozinc compound. The addition of CuCN · 2 LiCl followed by an excess of allyl bromide before hydrolysis did not afford any allylated product in the case of the alkyne **5** and led to a 1:1 mixture of the allylated and non-allylated **6** indicating a partial or complete loss of the metal during the cyclization. This can be explained by a radical mechanism. The radical cyclization of **5** promoted by Bu₃SnH (1.1 eq.) in benzene (0.05 N solution, AIBN cat. 80° C, 30 min) proceeds less efficiently than with zinc and affords a 58:42 ratio of the cyclized product **7** and of the reduced open-chain alkyne (1-phenylhexyne) in 65% yield; see (a) Beckwith, A.L.J.; Roberts, D.H. *J. Am. Chem. Soc.* **1986**, *108*, 5893 and references cited therein; (b) Porter, N.A.; Magnin, D.R.; Wright, B.T. *J. Am. Chem. Soc.* **1986**, *108*, 2787.
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11. Typical procedure: A THF solution of 3-cyano propylzinc iodide (7 mmol) was added at -10° C to a solution of 630 mg (7 mmol) of CuCN and of 590 mg (14 mmol) of LiCl in 8 mL of THF. The slightly green solution obtained, was cooled to -78° C and 2.5 mL (20 mmol) of Me₃SiCl and 490 mg (5 mmol) of ethyl propiolate was added. The reaction was allowed to warm to 23° C and stirred 17 hr. at this temperature. After the usual work-up, 1.00 g (4.2 mmol) of pure (E)-ethyl 6-cyano-2-trimethylsilyl-2-hexenoate (84% yield) was obtained. The stereochemistry of the double bond was established by an ¹H-NMR NOE experiment. (Irradiation of the vinylic proton at 6.18 ppm gave a strong enhancement of the methyl peak at 0.12 ppm).
12. (a) Chuit, C.; Foulon, J.P.; Normant, J.F. *Tetrahedron* **1981**, *27*, 1385; **1980**, *36*, 2305. (b) Bourgain-Commercon, M.; Foulon, J.P.; Normant, J.F. *J. Organomet. Chem.* **1982**, *228*, 321. (c) Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. (d) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. (e) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025. (f) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.
13. We verified that the formation of the C-silylated ester **12** is not due to the presence of zinc cations and the reaction of BuCu(CN)Li with **10c** in the presence of Me₃SiCl (2 equiv., 23° C, 24 hr.) affords the same ratio of **11**:**12** as observed with BuCu(CN)ZnI (entry 7).