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

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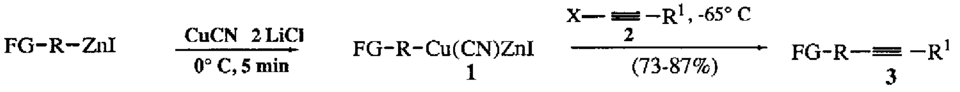
Summary: The highly functionalized organometallics RCu(CN)ZnI **1** react efficiently with 1-haloalkynes providing polyfunctionalized alkynes in high yields. This method has been used to prepare a pheromone of the *Amathes c-nigrum* in 3 steps and 64% overall yield. The reagents **1** also add in the presence of an excess of Me_3SiCl 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 polyfuntional 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 yields[5] (73-87%; see Scheme I and Table I). The best results are obtained by performing the reactions at low temperature (-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 carbocupration[6] 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

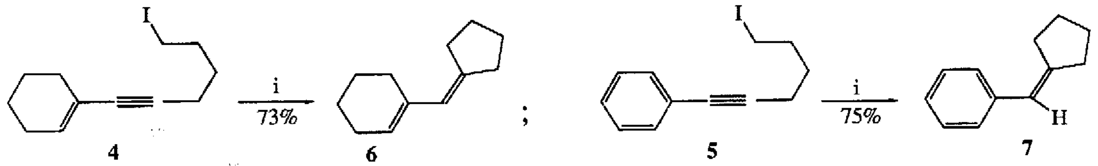
Scheme I



$$\text{FG-R-ZnI} \xrightarrow[0^\circ\text{ C, 5 min}]{\text{CuCN}\ 2\,\text{LiCl}} \underset{\mathbf{1}}{\text{FG-R-Cu(CN)ZnI}} \xrightarrow[(73\text{-}87\%)]{\underset{\mathbf{2}}{\text{X}-\!\equiv\!-\text{R}^1},\ -65^\circ\text{ C}} \underset{\mathbf{3}}{\text{FG-R}-\!\equiv\!-\text{R}^1}$$

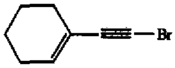
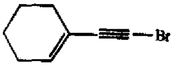
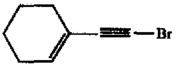
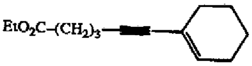
FG = ester, nitrile, alkyne, chloride X = I or Br

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**.

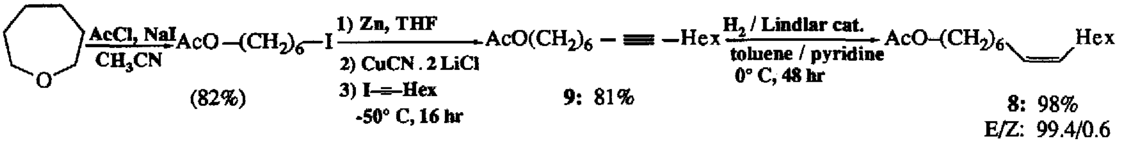
Entry	RCu(CN)ZnI	1-Haloalkyne	Products 3	Yield (%)[a]
1	$NC-(CH_2)_3-Cu(CN)ZnI$	$Br-{\equiv}-Hex$ **2a**	$NC-(CH_2)_3-{\equiv}-Hex$ **3a**	81
2	$EtO_2C-(CH_2)_3-Cu(CN)ZnI$	$Br-{\equiv}-Hex$ **2a**	$EtO_2C-(CH_2)_3-{\equiv}-Hex$ **3b**	78
3	c-HexCu(CN)ZnI	$Br-{\equiv}-Hex$ **2a**	c-Hex-≡-Hex **3c**	87
4	$CH_3-CH(OPiv)-(CH_2)_3-Cu(CN)ZnI$	$I-{\equiv}-Hex$ **2b**	$CH_3-CH(OPiv)-(CH_2)_3-{\equiv}-Hex$ **3d**	75
5	$NC-(CH_2)_3-Cu(CN)ZnI$	 **2c**	 **3e**	79
6	$Cl-(CH_2)_4-Cu(CN)ZnI$	 **2c**	 **3f**	81
7	$EtO_2C-(CH_2)_3-Cu(CN)ZnI$	 **2c**	 **3g**	74
8	$Pent-{\equiv}-(CH_2)_3-Cu(CN)ZnI$	$Ph-{\equiv}-Br$ **2d**	$Pent-{\equiv}-(CH_2)_3-{\equiv}-Ph$ **3h**	86
9	$EtO_2C-(CH_2)_3-Cu(CN)ZnI$	$Ph-{\equiv}-Br$ **2d**	$EtO_2C-(CH_2)_3-{\equiv}-Ph$ **3i**	73
10	$Cl-(CH_2)_4-Cu(CN)ZnI$	$Ph-{\equiv}-Br$ **2d**	$Cl-(CH_2)_4-{\equiv}-Ph$ **3j**	71

[a] Isolated yields of analytically pure products. Satisfactory spectral data (IR, ^1H and ^{13}C-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 ($CuCN \cdot 2\ LiCl$, 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 (H_2, 1 atm, $Pd/CaCO_3/PbO$; 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 both[11] (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 Me_3SiCl[12] 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 Me_3SiCl[12] 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

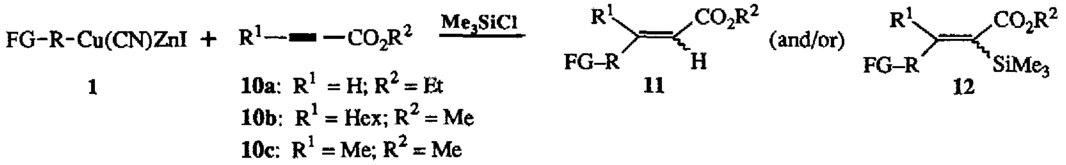
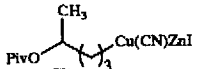
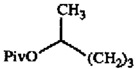
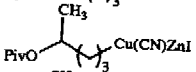
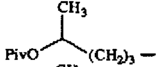
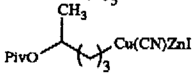
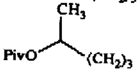


Table II. Ethylenic Esters **11** and **12** Obtained by the Addition of RCu(CN)ZnI **1** to the Acetylenic Esters **10a-c**.

Entry	FG–R–Cu(CN)ZnI	Acetylenic ester	No. of equiv. Me_3SiCl 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_2C–$(CH_2)_3$–Cu(CN)ZnI	**10a**	0	H	Et	EtO_2C–$(CH_2)_3$ –	100:0	99[b]
4	EtO_2C–$(CH_2)_3$–Cu(CN)ZnI	**10a**	4	H	Et	EtO_2C–$(CH_2)_3$–	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		**10b**	5	Hex	Me		100:0	77[c,f]
8		**10b**	4	Hex	Me		22:78	73[d,f]
9		**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 ^{13}C-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 $BF_3 \cdot OEt_2$. [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 Me_3SiCl 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 $BF_3 \cdot OEt_2$ does not improve this selectivity (see entry 10). Further synthetic applications of these and related reactions are currently being studied.

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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-iodobutane[2a] (40° C, 2 hr. then 23° C, 10 hr.), was added at -10° C to a solution of $CuCN \cdot 2\ LiCl$ (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 $CuCN \cdot 2\ LiCl$ 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 of **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 Bu_3SnH (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 alcyne (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 Me_3SiCl 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 ^{1}H-NMR NOE experiment. (Irradiation of the vinylic proton at 6.18 ppm gave a strong enhancement of the methyl peak at 0.12 ppm) .
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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 Me_3SiCl (2 equiv., 23° C, 24 hr.) affords the same ratio of **11:12** as observed with BuCu(CN)ZnI (entry 7).

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