The Reactivity of the Highly Functionalized Copper, Zinc Reagents

RCu(CN)ZnI Toward 1-Haloalkynes and Acetylenic Esters

Ming Chang P. Yeh and Paul Knochel*

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

Summary: The highly functionalized organometallics RCu(CN)ZnI 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 RZnX1,2 which can be converted to the corresponding copper derivatives RCu(CN)ZnX I 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-alkynes3,4 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 (-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 I

\[
\begin{align*}
\text{FG-} & \quad \text{R-} \quad \text{ZnI} \\
& \quad \text{CuCN} \quad 2 \text{LiCl} \\
& \quad 0^\circ \text{C, 5 min} \\
\rightarrow & \quad \text{FG-} \quad \text{R(CN)ZnI} \\
& \quad 1 \\
& \quad \text{X} \quad \text{R}^1, \quad -65^\circ \text{C} \\
& \quad 2 \quad \text{(73-87%)} \\
\rightarrow & \quad \text{FG-} \quad \text{R} \quad \text{R}^1 \\
& \quad 3 \\
\text{FG} & = \text{ester, nitrile, alkyne, chloride} \\
\text{X} & = \text{I or Br}
\end{align*}
\]

Scheme II

\[
\begin{align*}
& \quad \text{4} \quad \text{I} \\
& \quad \text{i} \quad \text{73%} \\
& \quad \text{6} \\
& \quad \text{5} \quad \text{I} \\
& \quad \text{i} \quad \text{75%} \\
& \quad \text{7} \\
\text{i:} & \quad \text{Zn (2.5 eq.), THF, 40°C, 1 hr, then 16 hr at 23°C}
\end{align*}
\]
Table I. Alkynes 3a-3j Obtained by the Reaction of RCu(CN)ZnI 1 with the 1-Haloalkynes 2a-2d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCu(CN)ZnI</th>
<th>1-Haloalkyne</th>
<th>Products 3</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NC-(CH₂)₃-Cu(CN)ZnI</td>
<td>Br-==Hex 2a</td>
<td>NC-(CH₂)₃-==Hex 3a</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>EtO₂C-(CH₂)₃-Cu(CN)ZnI</td>
<td>Br-==Hex 2a</td>
<td>EtO₂C-(CH₂)₃-==Hex 3b</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>c-HexCu(CN)ZnI</td>
<td>Br-==Hex 2a</td>
<td>c-Hex-==Hex 3e</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>CH₃-CH(OPiv)-(CH₂)₃-Cu(CN)ZnI</td>
<td>I-==Hex 2b</td>
<td>CH₃-CH(OPiv)-(CH₂)₃-==Hex 3d</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>NC-(CH₂)₃-Cu(CN)ZnI</td>
<td></td>
<td>NC-(CH₂)₃</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>Cl-(CH₂)₄-Cu(CN)ZnI</td>
<td></td>
<td>Cl-(CH₂)₄</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>EtO₂C-(CH₂)₃-Cu(CN)ZnI</td>
<td></td>
<td>EtO₂C-(CH₂)₃</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>Pent-==-(CH₂)₃-Cu(CN)ZnI</td>
<td>Ph-==Br 2d</td>
<td>Pent-==-(CH₂)₃-==Ph 3h</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>EtO₂C-(CH₂)₃-Cu(CN)ZnI</td>
<td>Ph-==Br 2d</td>
<td>EtO₂C-(CH₂)₃-==Ph 3i</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>Cl-(CH₂)₄-Cu(CN)ZnI</td>
<td>Ph-==Br 2d</td>
<td>Cl-(CH₂)₄-==Ph 3j</td>
<td>71</td>
</tr>
</tbody>
</table>

^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. This iodide was converted into 6-acetoxyhexylnzinc 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 10¹⁰ 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 Me₃SiCl 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 Me₃SiCl 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

\[ \text{AcCl}_{\text{Na}^+} \text{AcO}-(\text{CH}_2)_6^+ \rightarrow 1) \text{Zn, THF} \quad \text{AcO}-(\text{CH}_2)_6^+ \rightarrow \text{Hex}^+ \text{LiCl} \quad \text{toluene/pyridine} \quad \text{0°C, 48 hr} \quad \text{AcO}-(\text{CH}_2)_6^+ \text{Hex} \]

(82%)

Scheme IV

\[ \text{FG}^+\text{R}^-\text{Cu(CN)ZnI} + R^1 \rightarrow \text{CO}_2R^2 \quad \text{Me}_3\text{SiCl} \]

1

10a: R\(^1\) = H; R\(^2\) = Et
10b: R\(^1\) = Hex; R\(^2\) = Me
10c: R\(^1\) = Me; R\(^2\) = Me

Table II. Ethylenic Esters 11 and 12 Obtained by the Addition of R\(_2\text{Cu(CN)}\text{ZnI} 1\) to the Acetylenic Esters 10a-c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>FG-R-Cu(CN)ZnI</th>
<th>Acetylenic ester</th>
<th>No. of equiv. Me(_3)SiCl added</th>
<th>Products 11 and (or) 12</th>
<th>Ratio 11 : 12</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NC-(CH(_2))(_3)-Cu(CN)ZnI</td>
<td>10a</td>
<td>0</td>
<td>H Et NC-(CH(_2))(_3)-</td>
<td>100:0</td>
<td>83(^b)</td>
</tr>
<tr>
<td>2</td>
<td>NC-(CH(_2))(_3)-Cu(CN)ZnI</td>
<td>10a</td>
<td>4</td>
<td>H Et NC(CH(_2))(_3)-</td>
<td>0:100</td>
<td>84(^b)</td>
</tr>
<tr>
<td>3</td>
<td>EtO(_2)C-(CH(_2))(_3)-Cu(CN)ZnI</td>
<td>10a</td>
<td>0</td>
<td>H Et EtO(_2)C-(CH(_2))(_3)-</td>
<td>100:0</td>
<td>99(^b)</td>
</tr>
<tr>
<td>4</td>
<td>EtO(_2)C-(CH(_2))(_3)-Cu(CN)ZnI</td>
<td>10a</td>
<td>4</td>
<td>H Et EtO(_2)C-(CH(_2))(_3)-</td>
<td>0:100</td>
<td>91(^b)</td>
</tr>
<tr>
<td>5</td>
<td>Cl-(CH(_2))(_4)-Cu(CN)ZnI</td>
<td>10a</td>
<td>4</td>
<td>H Et Cl-(CH(_2))(_4)-</td>
<td>0:100</td>
<td>85(^b)</td>
</tr>
<tr>
<td>6</td>
<td>NC-(CH(_2))(_3)-Cu(CN)ZnI</td>
<td>10b</td>
<td>2</td>
<td>Hex Me NC-(CH(_2))(_3)-</td>
<td>100:0</td>
<td>82(^f)</td>
</tr>
<tr>
<td>7</td>
<td>PivOCH(_3)(_3)-Cu(CN)ZnI</td>
<td>10b</td>
<td>5</td>
<td>Hex Me PivOCH(CH(_2))(_3)-</td>
<td>100:0</td>
<td>77(^c,f)</td>
</tr>
<tr>
<td>8</td>
<td>PivOCH(_3)(_3)-Cu(CN)ZnI</td>
<td>10b</td>
<td>4</td>
<td>Hex Me PivOCH(CH(_2))(_3)-</td>
<td>22:78</td>
<td>73(^d,f)</td>
</tr>
<tr>
<td>9</td>
<td>PivOCH(_3)(_3)-Cu(CN)ZnI</td>
<td>10c</td>
<td>4</td>
<td>Me Me PivOCH(CH(_2))(_3)-</td>
<td>12:88</td>
<td>78(^f)</td>
</tr>
<tr>
<td>10</td>
<td>AcO-(CH(_2))(_6)-Cu(CN)ZnI</td>
<td>10c</td>
<td>1.6</td>
<td>Me Me AcO-(CH(_2))(_6)-</td>
<td>17:81</td>
<td>76(^e,f)</td>
</tr>
<tr>
<td>11</td>
<td>BuCu(CN)ZnI</td>
<td>10c</td>
<td>4</td>
<td>Me Me Bu</td>
<td>9:91</td>
<td>85(^f)</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields of analytically pure products. Satisfactory spectral data (IR, \(^1\)H 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\(_3\)·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$_3$SiCl 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$_3$ · OEt$_2$ 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.


5. Typical procedure: A THF solution of 4-chlorobutylzinc iodide (7 mmol), 1.4 eq. prepared in over 90% from dchloro-1-iodobutane$^{2a}$ (40° C, 2 hr. then 23° C, 10 hr.), was added at -10° C to a solution of CuCN and of LiCl in 8 mL of THF. The slightly green solution obtained, was allowed to warm to 23° C and stirred 17 hr. at this temperature. After the usual work-up and purification by flash chromatography (solvent: hexane), 800 mg of pure 3f was obtained (81% yield).


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 alkynyl 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$_3$SnH (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.; Magini, D.R.; Wiig,A. B.T. J. Am. Chem. Soc. 1986, 108, 2787.


11. Typical procedure: A THF solution of 3-cyano propylzinc iodide (7 mmol) was added at -10° C to a solution of CuCN · 2 LiCl in 8 mL of THF. The slightly green solution obtained, 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 ethyl propiolate was 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).


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$_3$SiCl (2 equiv., 23° C, 24 hr.) affords the same ratio of 11:12 as observed with BuCu(CN)ZnI (entry 7).

(Received in USA 3 May 1989)