Pergamon

Tetrahedron Letters 40 (1999) 5115–5118

TETRAHEDRON
LETTERS

# Addition of Z-vinylic higher order cyanocuprates to hindered enones. The influence of the reaction conditions

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Received 12 April 1999; revised 6 May 1999; accepted 10 May 1999

## Abstract

Z-Vinylic higher order cyanocuprates, prepared from the corresponding Z-vinylic tellurides, react efficiently with hindered enones in THF/$BF_3 \cdot Et_2O$ or in diethyl ether. In neat THF the hindered enones fail to react with Z-vinyl cyanocuprates prepared in this way. © 1999 Elsevier Science Ltd. All rights reserved.

*Keywords:* Z-vinylic higher order cyanocuprates; Z-vinylic tellurides; hindered enones.

The generation of Z-vinylic higher order cyanocuprates through transmetallation reactions is not a straightforward process.[1] We found that the hydrotelluration of acetylenes followed by transmetallation with easily accessible higher order cyanocuprates is an alternative for the existing methods to generate such species.[2] This reaction sequence was recently used by us in a key step of the total synthesis of Macrolactin A,[3] a potent anti-viral agent.[4] A serious drawback of our methodology was the inertness of hindered enones towards the Z-vinylic higher order cyanocuprates.[2]

In this communication we report that this problem can be overcome by changing the reaction conditions. When telluride **1a** was transmetallated at room temperature with higher order cyanocuprate **3** (route (a),[5] Scheme 1) followed by reaction of the intermediate Z-vinylic cyanocuprate **5** in THF with isophorone **6a** at −78°C with subsequent heating to room temperature, only traces of the 1,4-addition product **7** were formed. The yield of **7** increased to 70% when borontrifluoride etherate was added to the reaction mixture (Scheme 1). A similar result was obtained using diethyl ether as the solvent in the presence or in the absence of $BF_3 \cdot Et_2O$.

Route (a) in Scheme 1 also constitutes an easy and straightforward way to prepare the Z-vinyl 2-thienyl cyanocuprate **5**. In our previous work this cuprate was prepared via several steps requiring at least 2 h.[2d] The present methodology furnishes the desired cuprate **5** in half this time and in only one step.

By route (b)[6] (Scheme 1) the vinyl cuprate **5** was formed by reaction of the butyl vinyl telluride **2a** with the mixed cyanocuprate **4**. In this case the reaction was only performed in THF/$BF_3 \cdot Et_2O$, since the reaction mixture becomes insoluble in diethyl ether at low temperature (Table 1).

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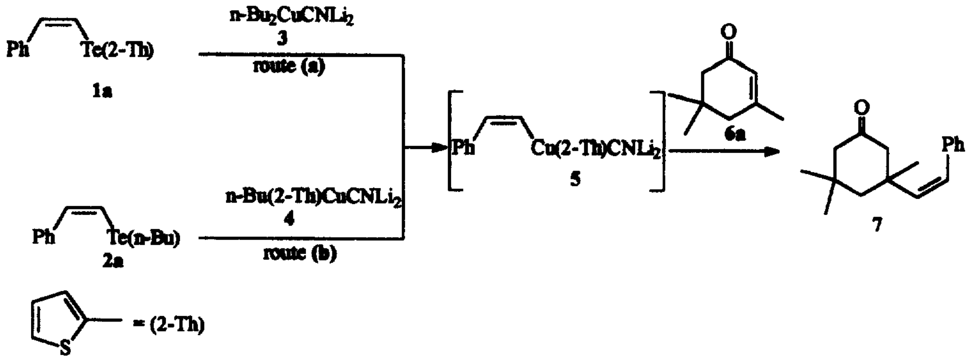
*PII:* S0040-4039(99)00951-X



| Conditions | Yield (%) |
|---|---|
| THF | Trace |
| THF/ $BF_3{\bullet}Et_2O$ | 70 |
| $Et_2O$/ $BF_3{\bullet}Et_2O$ | 66 |
| $Et_2O$ | 72 |

Scheme 1.

The product **7c** has shown a synthetic potential due to the presence of the protective group trimethylsilyl (TMS), which can be easily removed in order to be functionalized.[7] In this way, the starting telluride **2c** has been used as a key intermediate in the synthesis of the anti-fungal agent Siphonodiol.[8]

In summary, with the improvements described in this communication, the 1,4-addition of *Z*-vinylic higher order cyanocuprates (derived from *Z*-vinylic tellurides) to enones becomes a synthetic route of general scope. Furthermore, the use of 2-thienyl vinyl tellurides to generate the higher order vinyl cyanocuprates makes the method more convergent.

## Acknowledgements

The authors thank FAPESP, CNPq and CAPES for Financial support. We thank Prof. Jose M. Riveros for the critical revision of the manuscript.

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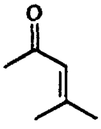
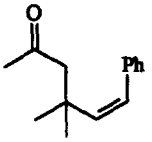
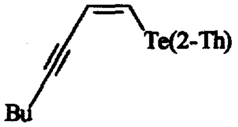
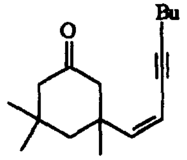
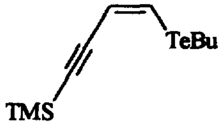
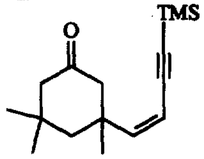
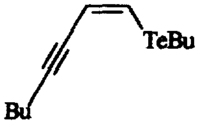
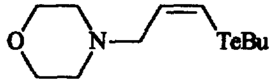
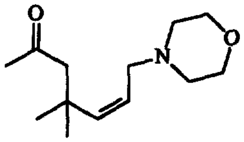
5. *Typical procedure*: the vinyl 2-thienyl cyanocuprate **5** (2 mmol) was prepared starting from the vinyl 2-thienyl telluride **1b** as described in reference 2d. To the solution of **5** cooled to –78°C were added simultaneously isophorone **6a** (0.276 g, 2.2 mmol) and $BF_3 \cdot Et_2O$ (0.28 mL, 2.2 mmol) at one time. The reaction mixture was allowed to reach the room temperature and then worked up as described in reference 2d. Purification of **7a** was performed by silica gel column chromatography eluting with a 9:1 mixture of hexane:ethyl acetate. Yield: 0.344 g (70%) $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ (ppm) 0.90–0.96

Table 1

| Entry | Telluride | Enone | Product a,c | Yield (%) b |
|---|---|---|---|---|
| 1 |  2 a |  6 b |  7 a | 65 |
| 2 |  1 b | 6 a |  7 b | 70 |
| 3 |  2 c | 6 b |  7 c | 81 |
| 4 |  2 b | 6 a | 7 b | 71 |
| 5 |  2 d | 6 b |  7 d | 70 |

**a) All the reactions were performed in THF / $BF_3{\bullet}Et_2O$; b) Yields of the isolated products purified by silica gel column chromatography eluting with mixtures of hexane:ethyl acetate; c) All the products were isolated as pale yellow oils.**

(m, 6H), 1.05 (s, 3H), 1.34 (s, 3H), 1.42–1.60 (m, 6H), 2.16 (dt, *J*=7.3, 2.2 Hz, 2H), 2.33–2.48 (m, 2H), 2.73 (d, *J*=13.24 Hz, 1H), 5.40 (dt, *J*=11.76, 2.2 Hz, 1H), 5.73 (d, *J*=12.50 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ (ppm) 13.5, 19.3, 22.0, 29.2, 29.8, 30.6, 32.4, 36.1, 41.3, 49.1, 53.1, 54.3, 98.6, 108.9, 147.8, 211.4; LRMS *m/z* (rel. int.) 231 (38), 203 (38), 175 (100), 161 (76), 147 (86), 133 (77), 119 (93), 105 (80), 91 (59), 77 (21), 55 (12); IR (neat) ν ($cm^{-1}$) 740, 1229, 1281, 1714, 2869, 2932, 2956, 3024; Anal. calcd for $C_{17}H_{26}O$: C, 82.86; H, 10.64; found: C, 82.76; H, 10.56.

6. *Typical procedure*: the vinyl 2-thienyl cyanocuprate **5** (2 mmol) was prepared starting from the butyl vinyl telluride **2c** as described in reference 2d. Isophorone **6a** (0.276 g, 2.2 mmol) and $BF_3{\cdot}Et_2O$ (0.28 mL, 1.1 mmol) were added to the solution of **5** as described above and the reaction mixture was worked up as described in reference 2d. Purification of 7c was performed by silica gel column chromatography eluting with a 9:1 mixture of hexane:ethyl acetate. Yield: 0.46 g (81%) $^1H$ NMR (500 MHz, $CDCl_3$) δ (ppm), *J* (Hz) 0.18 (s, 9H), 0.95 (s, 3H), 1.04 (s, 2H), 1,34 (s, 3H), 1.56 (s, 6H),

2.17 (s, 4H), 5.41 (d, 12.0, 1H), 5.85 (d, 12.0, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ (ppm) 0.31, 29.10, 29.61, 32.35, 36.23, 41.68, 48.59, 100.01, 101.12, 108.57, 150.99, 211.28; LRMS *m/z* (rel. int.) 262 (15), 247 (59), 206 (6), 191 (43), 177 (65), 161 (34), 123 (17), 83 (26), 73 (100); IR (neat) ν (cm$^{-1}$): 846, 1251, 1714, 2150, 2959; HRMS exact mass calcd for $C_{26}H_{16}OSi$: 262.17529; found: 262.17517.

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