Notiz / Note

anti-Michael Addition of Cyanocuprate *t*BuCu(CN)Li to Acceptor-Substituted Enynes

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Acceptor-substituted enynes **1** react with lithium *tert*-butylcyanocuprate [*t*BuCu(CN)Li] in THF to afford *anti*-Michael adducts **3**. The formation of the isomeric side products **4** can be suppressed by regioselective protonation of the organometallic intermediates with ethanol at −80°C. Evidence for radical intermediates or electron-transfer steps in these reactions could not be obtained.

The formation of products with a formal *anti*-Michael regioselectivity in addition reactions of nucleophiles with Michael acceptors has been observed very rarely, e.g. in reactions of *tert*-butylmagnesium chloride with cinnamates[1] and of organolithium compounds (in particular *t*BuLi) with acrylic esters, acrylic amides, and acetylenic amides[2]. This unusual regioselectivity was attributed to the addition of free *tert*-butyl radicals (formed by single-electron transfer) to the Michael acceptors. In contrast to this, *anti*-Michael additions of organocuprates have not been reported so far, although they represent the most important reagents in conjugate addition reactions[3]. In this paper we describe our results on *anti*-Michael additions of lithium *tert*-butylcyanocuprate [*t*BuCu(CN)Li] to acceptor-substituted enynes.

The 1,6-addition reaction of organocuprates with 2-en-4-ynoates usually readily provides β-allenic esters of type **2**[4] as the only products[5], in particular if lithium di-*tert*-butylcyanocuprate [tBu$_2$Cu(CN)Li$_2$] is used[6]. In a few cases, however, we noticed the formation of side products **3**–**5** in these reactions, i.e. *anti*-Michael (**3**, **4**) and 1,4-addition products (**5**). Careful reexamination of these transformations revealed that small deviations from the 2:1 stoichiometry of *t*BuLi and CuCN necessary to obtain tBu$_2$Cu(CN)Li$_2$ led to the inadvertent formation of products **3**–**5**. In order to gain a better understanding of this result, we treated enynoate **1a** with reagents formed from different ratios of *t*BuLi and CuCN (Table 1).

Table 1. Composition of product mixtures (%) obtained from the reaction of enynoate **1a** with cyanocuprates tBu$_n$Cu(CN)Li$_n$

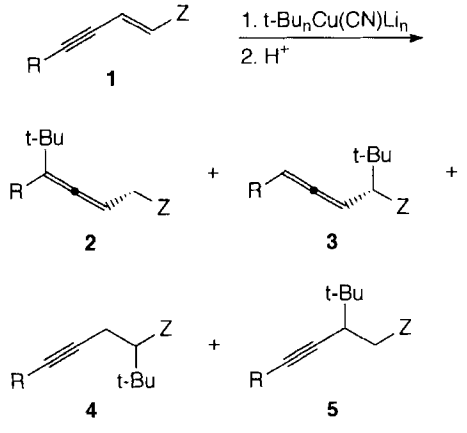
n	Solvent	**1a**	**2a**	**3a**[a]	**4a**	**5a**
1.1	THF	2	0	33/34	24	7
1.6	THF	4	44	17/23	7	5
1.9	THF	0	79	6/7	4	4
2.0	THF	0	100	0	0	0
2.4	THF	0	92	0	0	8
1.1	Et_2O	14	4	14/40	12	16
1.1	*t*BuOMe	22	19	5/15	4	35

[a] Two diastereomers.

1a: R = t-Bu, Z = CO_2Et

1b: R = Ph, Z = CO_2Et

1c: R = t-Bu, Z = CN



As described earlier[6], 1,6-adduct **2a** is the only product if the reaction is carried out with a 2:1 stoichiometry of *t*BuLi and CuCN, regardless whether diethyl ether[6] or THF is used as solvent. Strikingly, the formation of side products already starts if the reaction is carried out with a ratio of *t*BuLi:CuCN = 1.9:1 in THF; even with this small deviation from the ideal stoichiometry of tBu$_2$Cu(CN)Li$_2$, compounds **3**–**5** represent 21% of the crude product mixture. With decreasing amounts of *t*BuLi, the portion of allenes **3** and alkynes **4**/**5** increases further. Use of a 1.1:1 ratio of *t*BuLi:CuCN, i.e. nearly the composition of lithium *tert*-butylcyanocuprate [*t*BuCu(CN)Li], in THF gives the *anti*-Michael adducts **3a** and **4a** as main products, accompanied by small amounts of starting material (**1a**) and 1,4-adduct **5a**; under these conditions, 1,6-addition product **2a** is not formed any more! The reactivity of *t*BuCu(CN)Li towards enynonate **1a** is affected only slightly by the solvent; in diethyl ether or *tert*-butyl methyl ether, the *anti*-Michael

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adducts are still the major products, although the reaction is not as selective as in THF. In contrast to this, with ratios of *t*BuLi:CuCN > 2:1 in THF, the 1,6-adduct **2a** is the major product, and the only side product observed is 1,4-adduct **5a**, probably formed by addition of free *t*BuLi to enynoate **1a** (only two equivalents of *t*BuLi can be bound in the cuprate cluster by one equivalent of CuCN[3]).

Thus, it seems possible to control the course of the reaction of acceptor-substituted enynes with *tert*-butylcuprates by the stoichiometry of the reagent: treatment with $tBu_2Cu(CN)Li_2$ furnishes the 1,6-addition product **2** exclusively, whereas with *t*BuCu(CN)Li *anti*-Michael adducts **3** and **4** are mainly formed. The latter products are probably obtained from the same organometallic intermediate by protonation at C-3 (to give alkyne **4**) or at C-5 (to give allenes **3**); a similar scheme was already observed in conjugate reduction reactions of enynoates[7]. Therefore, in analogy to our earlier results on regioselective protonations of allenyl enolates[5a,b], it could be possible to influence the ratio of **3**:**4** by variation of the proton source. Indeed, the ratio of **3a**:**4a** = 2.8:1 obtained by protonation with water at 0°C could be improved to 11:1 upon protonation with ethanol at −80°C. However, the stereoselectivity of the formation of the two diastereomers of allene **3a** depends only slightly on the proton source (water, 0°C: ds = 1:1; ethanol, −80°C: ds = 7:3).

On a preparative scale, allenes **3a** were obtained in 70% yield by treatment of enynoate **1a** with *t*BuCu(CN)Li and low-temperature protonation with ethanol. Likewise, the phenyl-substituted substrate **1b** gave allenes **3b** (77% yield, ds = 1:1). Interestingly, this method could also be applied to enynenitrile **1c**, a Michael acceptor that does not undergo 1,6-addition reactions with $tBu_2Cu(CN)Li_2$[5a,8]. Reaction with *t*BuCu(CN)Li and protonation with ethanol provided allenic nitriles **3c** (ds = 78:22) in 48% yield. In contrast to these acceptor-substituted enynes, methyl cinnamate reacts very sluggishly with *t*BuCu(CN)Li to give a mixture of the Michael and *anti*-Michael adducts.

From the mechanistic point of view, it is crucial to note that the formation of *anti*-Michael products is specific to the *tert*-butylcyanocuprate *t*BuCu(CN)Li; the corresponding methyl- and *n*-butyl-substituted cuprates with a 1:1 stoichiometry of RLi and CuCN do not react with enynoate **1a**. In order to establish whether the reactions of *t*BuCu(CN)Li take place via radical intermediates, as has been suggested for *anti*-Michael additions of Grignard[1] and organolithium reagents[2], the radical trap 2,2,6,6-tetramethylpiperidin-1-yloxy (TMPO) was added to the reaction mixture. The only trapping product isolated in this reaction was the *N*-*tert*-butoxypiperidine derivative; since this is also formed from *tert*-butylcuprates and TMPO in the absence of a substrate[9], the observation of this product is not indicative of a radical mechanism. Likewise, the addition of nitrobenzene which is known to suppress electron-transfer processes[10] did not affect the formation of *anti*-Michael products in the reaction of enynoate **1a** with *t*BuCu(CN)Li. Finally, an interesting behavior was encountered when the reaction of **1a** with *t*BuCu(CN)Li in THF was quenched with D_2O: The amount of deuterium incorporated into the product depends on the reaction temperature. When the reaction was carried out at −80°C and the reaction mixture hydrolyzed at this temperature with D_2O, the *anti*-Michael product **3a** contained ca. 80% deuterium; if the mixture was warmed up to −30°C before quenching, the incorporation of deuterium decreased to ca. 50%. Obviously, an organolithium intermediate is formed in the *anti*-Michael addition which at elevated temperatures is protonated by the solvent THF.

To summarize, it has been shown that *anti*-Michael adducts **3** can be obtained by reaction of acceptor-substituted enynes **1** with lithium *tert*-butylcyanocuprate *t*BuCu(CN)Li. The formation of the isomeric side products **4** can be suppressed by regioselective protonation of the organometallic intermediates with ethanol at −80°C. Evidence for radical intermediates or electron-transfer steps in these reactions could not be obtained.

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Experimental

General Information: See ref.[5a].

Reaction of Ethyl 6,6-Dimethyl-2-hepten-4-ynoate (**1a**) *with Cyanocuprates* $tBu_nCu(CN)Li_n$: To a suspension of 90 mg (1.0 mmol) of CuCN in 2 ml of the solvent (THF, Et_2O, or MeO*t*Bu) was added dropwise at −30°C *n* mmol of *t*BuLi (1.7 M solution in pentane). The mixture was stirred for 15 min at −30°C, cooled to −80°C, and treated with 162 mg (0.9 mmol) of **1a**[11] in 0.5 ml of the solvent. After stirring for 30 min at −80°C, the mixture was warmed to 0°C, and 2 ml of water was added. The copper salts were removed by filtration through Celite, and the composition of the crude product was examined by GC (OV-1701, H_2). Elution order: **1a**, **5a**, **3a** (diastereomer 1), **4a**, **3a** (diastereomer 2), **2a**. Allenes **2a**[6] and **3a** (see below) were identified by their NMR spectra. The 1,4-adduct **5a** was prepared independently by reaction of **1a** with *t*BuLi and *t*BuCu/Me_3SiI[12], respectively.

Ethyl 6,6-Dimethyl-2-(1,1-dimethylethyl)-4-heptynoate (**4a**): ^1H NMR: δ = 0.88 [s, 9H, $C(CH_3)_3$], 1.08 [s, 9H, $C(CH_3)_3$], 1.22 (t, *J* = 7.1 Hz, 3H, CH_3), 2.20 (dd, *J* = 2.5/14.2 Hz, 1H, 3-H), 2.31 (dd, *J* = 2.5/11.4 Hz, 1H, 2-H), 2.42 (dd, *J* = 11.4/14.2 Hz, 1H, 3-H), 4.05 (q, *J* = 7.1 Hz, 2H, CH_2).

Ethyl 6,6-Dimethyl-3-(1,1-dimethylethyl)-4-heptynoate (**5a**): ^1H NMR: δ = 1.15 [s, 9H, $C(CH_3)_3$], 1.26 [s, 9H, $C(CH_3)_3$], 1.28 (t, *J* = 7.1 Hz, 3H, CH_3), 2.26 (dd, *J* = 10.9/14.2 Hz, 1H, 2-H), 2.48 (dd, *J* = 4.5/14.2 Hz, 1H, 2-H), 2.55 (dd, *J* = 4.5/10.9 Hz, 1H, 3-H), 4.19 (q, *J* = 7.1 Hz, 2H, CH_2).

Ethyl 6,6-Dimethyl-2-(1,1-dimethylethyl)-3,4-heptadienoate (**3a**): To a suspension of 180 mg (2.0 mmol) of CuCN in 4 ml of THF was added dropwise at −30°C 1.2 ml (2.0 mmol) of *t*BuLi (1.7 M solution in pentane). After stirring for 15 min at −30°C, the mixture was cooled to −80°C and a solution of 180 mg (1.0 mmol) of **1a**[11] in 1 ml of THF was added. The mixture was warmed to −40°C during 1 h and then cooled back to −80°C; the reaction was quenched by addition of 5 ml of a cold (−80°C) 2 M solution of ethanol in diethyl ether. The mixture was warmed to room temperature, then 5 ml of water was added, and the copper salts were removed by filtration through Celite. The filtrate was concentrated in vacuo, and the crude product was purified by column chromatography [SiO_2; diethyl ether/hexane (1:20)], giving 165 mg (70%) of **3a** (70:30 mixture of diastereomers) as a colorless liquid. − IR: $\tilde{\nu}$ = 1970 cm^{-1} (C=C=C), 1740 (s, C=O). − ^1H NMR: Major diastereomer: δ = 1.01 [s, 9H, $C(CH_3)_3$], 1.04 [s, 9H, $C(CH_3)_3$], 1.26 (t, *J* = 7.1 Hz, 3H, CH_3), 2.78 (dd, *J* = 0.8/10.0 Hz, 1H, 2-H), 4.13/4.14 (2 q, 2 × *J* = 7.1 Hz, 2H, CH_2), 5.15 (dd, *J* = 0.8/6.2 Hz, 1H, 5-H), 5.30 (dd, *J* = 6.2/10.0 Hz, 1H, 3-H); minor diastereomer: δ = 0.99 [s, 9H, $C(CH_3)_3$], 1.02 [s, 9H, $C(CH_3)_3$], 1.26 (t, *J* = 7.2 Hz, 3H, CH_3), 2.77 (dd, *J* = 1.2/9.6 Hz, 1H, 2-H), 4.14/4.15 (2 q, 2 × *J* = 7.2 Hz, 2H, CH_2), 5.14 (dd, *J* = 1.2/6.2 Hz, 1H, 5-H), 5.25 (dd, *J* = 6.2/9.6 Hz, 1H, 3-H). − ^{13}C NMR: Major diastereomer: δ = 14.1 (+, CH_3), 27.8 [+, $C(CH_3)_3$], 30.3 [+, $C(CH_3)_3$], 31.8 [×, $C(CH_3)_3$], 33.7 [×, $C(CH_3)_3$], 57.4 (+, C-2), 60.1 (−, CH_2), 89.2 (+, C-3), 103.4 (+, C-5), 173.2 (×, C-1), 202.0 (×,

C-4); minor diastereomer: δ = 14.3 (+, CH_3), 27.5 [+, C(CH_3)$_3$], 30.1 [+, C(CH_3)$_3$], 31.6 [×, $C(CH_3)_3$], 34.0 [×, $C(CH_3)_3$], 57.4 (+, C-2), 60.0 (−, CH_2), 89.3 (+, C-3), 103.2 (+, C-5), 173.2 (×, C-1), 202.4 (×, C-4). − MS: *m/z* (%) = 238 (1) [M^+], 181 (100). − $C_{15}H_{30}O_2$ (238.4): calcd. C 75.58, H 10.99; found C 75.71, H 11.12.

Ethyl 5-Phenyl-2-(1,1-dimethylethyl)-3,4-pentadienoate (**3b**): Prepared from 180 mg (2.0 mmol) of CuCN in 4 ml of THF, 1.2 ml (2.0 mmol) of *t*BuLi, and 200 mg (1.0 mmol) of **1b**[5a] in 1 ml of THF as described for **3a**. Yield: 198 mg (77%) of **3b** (1:1 mixture of diastereomers) as a colorless oil. − IR: $\tilde{\nu}$ = 1960 cm^{-1} (C=C=C), 1735 (s, C=O). − ^{1}H NMR: Diastereomer 1: δ = 1.06 [s, 9H, C(CH_3)$_3$], 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 2.94 (dd, *J* = 0.8/10.0 Hz, 1H, 2-H), 4.12/4.13 (2 q, 2 × *J* = 7.1 Hz, 2H, CH_2), 5.71 (dd, *J* = 6.4/10.0 Hz, 1H, 3-H), 6.18 (dd, *J* = 0.8/6.4 Hz, 1H, 5-H), 7.14−7.24 (m, 1H, Ph), 7.25−7.28 (m, 4H, Ph); diastereomer 2: δ = 1.04 [s, 9H, C(CH_3)$_3$], 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 2.94 (dd, *J* = 1.2/9.6 Hz, 1H, 2-H), 4.15/4.16 (2 q, 2 × *J* = 7.1 Hz, 2H, CH_2), 5.72 (dd, *J* = 6.4/9.6 Hz, 1H, 3-H), 6.17 (dd, *J* = 1.2/6.4 Hz, 1H, 5-H), 7.14−7.24 (m, 1H, Ph), 7.25−7.28 (m, 4H, Ph). − ^{13}C NMR: δ = 14.6/14.7 (2+, CH_3), 28.0/28.2 [2+, C(CH_3)$_3$], 34.2/34.7 [2×, $C(CH_3)_3$], 56.9/57.4 (2+, C-2), 60.7 (−, CH_2), 91.9/92.1/95.3/95.4 (4+, C-3, C-5), 127.0/127.1/127.2/127.5/128.7/128.9 (6+, Ph), 134.5/134.7 (2×, Ph), 173.1/173.3 (2×, C-1), 206.2/206.6 (2×, C-4). − MS: *m/z* (%) = 258 (4) [M^+], 173 (100). − $C_{17}H_{22}O_2$ (258.4): calcd. C 79.03, H 8.58; found C 79.21, H 8.93.

6,6-Dimethyl-2-(1,1-dimethylethyl)-3,4-heptadiennitrile (**3c**): Prepared from 360 mg (4.0 mmol) of CuCN in 8 ml of THF, 2.4 ml (4.0 mmol) of *t*BuLi, and 220 mg (1.7 mmol) of **1c**[11] in 1 ml of THF as described for **3a**. Purification by column chromatography [SiO_2; diethyl ether/hexane (1:20)] furnished 158 mg (48%) of **3c** (78:22 mixture of diastereomers) as a slightly yellow oil. − IR. $\tilde{\nu}$ = 2235 cm^{-1} (CN), 1965 (C=C=C). − ^{1}H NMR: Major diastereomer: δ = 1.01 [s, 18H, C(CH_3)$_3$], 2.93 (dd, *J* = 2.6/6.8 Hz, 1H, 2-H), 5.08 (dd, *J* = 6.2/6.8 Hz, 1H, 5-H), 5.30 (dd, *J* = 2.6/6.2 Hz, 1H, 3-H); minor diastereomer: δ = 1.01 [s, 18H, C(CH_3)$_3$], 2.91 (dd, *J* = 2.0/7.5 Hz, 1H, 2-H), 5.09 (dd, *J* = 6.2/7.5 Hz, 1H, 5-H), 5.30 (dd, *J* = 2.0/6.2 Hz, 1H, 3-H). − ^{13}C NMR: Major diastereomer: δ = 26.2 [+, C(CH_3)$_3$], 29.1 [+, C(CH_3)$_3$], 31.2 [×, $C(CH_3)_3$], 33.2 [×, $C(CH_3)_3$], 45.0 (+, C-2), 86.7 (+, C-3), 105.2 (+, C-5), 119.3 (×, C-1), 202.6 (×, C-4); minor diastereomer: δ = 26.2 [+, C(CH_3)$_3$], 29.1 [+, C(CH_3)$_3$], 31.1 [×, $C(CH_3)_3$], 34.2 [×, $C(CH_3)_3$], 44.7 (+, C-2), 86.7 (+, C-3), 105.3 (+, C-5), 119.4 (×, C-1), 202.7 (×, C-4). − MS: *m/z* (%) = 191 (4) [M^+], 57 (100). − $C_{15}H_{21}N$ (191.3): calcd. C 81.62, H 11.06, N 7.32; found C 81.12, H 11.08, N 7.15.

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