1,6-Reduction of 2-En-4-ynoates Using Lithium Di-s-butylcyanocuprate

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Abstract: Treatment of 2-en-4-ynoates 1 with lithium di-s-butylcyanocuprate in diethyl ether yields the 1,6-reduction products 2, whereas in tetrahydrofuran the 1,6-addition products 4 are obtained.

Organocuprates represent an excellent example for a dilemma frequently encountered in Organic Chemistry: they are among the most commonly used reagents, and yet the understanding of the mechanisms of their reactions is poor. The synthetic use of cuprates in addition and substitution reactions is well established¹); in contrast to this, a third class of organocuprate reactions is generally neglected, i.e. the potential of cuprates to induce reduction processes. The mostly undesired formation of reduction products in reactions of organocuprates was explained by the ability of these reagents to react under electron transfer²) or in terms of the formation of copper hydride species by reductive elimination of organocuprates bearing β-hydrogen atoms³). However, to the best of our knowledge, there is only a small number of synthetic applications of organocuprate reductions^{2g}).

During our investigation of the 1,6-addition of organocuprates to acceptor-substituted enynes⁴) we noticed in some cases the formation of side products that are formally derived from nucleophilic attack of a hydride ion to C-5 of the enyne, i.e. a 1,6-reduction of the enyne is taking place. Whereas with lithium dimethylcuprate, lithium di-n-butylcyanocuprate and lithium di-t-butylcyanocuprate only small amounts of these products are formed, the 1,6-reduction is the main reaction if lithium di-s-butylcyanocuprate is used. Thus, reaction of ethyl 5-phenyl-2-penten-4-ynoate (1a) with s-Bu₂Cu(CN)Li₂, prepared from commercially available s-BuLi (Aldrich), in diethyl ether at -20°C and quenching with pivalic acid at -80°C (in order to achieve regioselective protonation at C-2⁴) gave the 1,6-reduction product, allene 2a, in 30% yield, accompanied by 10% of 1,4-reduction (3a) and 16% of 1,6-addition (4a) products⁵).

The product ratio depends also on the substitution pattern of the starting enyne: if the enynoate **1c** with a methyl group at C-3 is treated with s-Bu₂Cu(CN)Li₂ under the same conditions, both the 1,4-reduction and the 1,6-addition are retarded, and the allene **2c** is isolated in 39% yield as the sole product. Thus, this method is synthetically valuable for the synthesis of allenes with a variable substitution pattern.



A striking change in the reactivity of lithium di-s-butylcyanocuprate towards 2-en-4-ynoates **1** is observed if the solvent is changed from diethyl ether to tetrahydrofuran: now the 1,6-addition product **4** is the main product of the reaction. Starting with the phenyl-substituted enynoate **1a**, adduct **4a** is isolated in 31% yield, whereas with enynoate **1b** a mixture of **4b** (56%) and **2b** (9%) is obtained⁵). It is well established that the solvent as well as added salts have a strong influence on the structures and consequently on the reactivity of organocuprates^{4,6}). Nevertheless, the observed shift in the product spectrum towards 1,6-addition by changing the solvent to THF is surprising because it was found earlier that the 1,6-addition of organocuprates to acceptor-substituted enynes in THF is very slow or does not take place at all⁴).

To the best of our knowledge, no example of a 1,6-reduction of acceptor-substituted 2-en-4-ynes has been reported yet; in contrast to this, there has been considerable effort to develop methods for the 1,4-reduction of α , β -unsaturated carbonyl compounds. The following reagents have been used for this purpose: LiAlH₄ – Cul⁷), LiAlH(OMe)₃ – CuBr⁸), MeCu – DIBAH – HMPA⁹) (also effective for the 1,6-reduction of 2,4-dienones and 2,4-dienoates), t-BuCu – DIBAH¹⁰), [(Ph₃P)CuH]₆¹¹), Bu₃SnH – Cul – Me₃SiCl¹²), and NaBH₄ – Cu₂Cl₂¹³). In order to examine the potential of these reagents for 1,6-reduction of 2-en-4-ynoates, ester **1a** was treated with some of them. Reaction of **1a** with LiAlH₄ – Cul⁷) gave 5-phenyl-2-penten-4-yn-1-ol and 5-phenyl-4-pentyn-1-ol, i.e. reduction of the ester group and of the double bond of **1a**. Treatment of **1a** with MeCu – DIBAH – HMPA⁹) yielded a 1:1 mixture of 1,6-(**2a**) and 1,4-reduction (**3a**) products, whereas no reaction of **1a** with Bu₃SnH – Cul – Me₃SiCl¹²) occurred. Thus, these reagents are unsuitable for an effective 1,6-reduction of 2-en-4-ynoates.

In order to draw conclusions on the mechanism of the reduction of 2-en-4-ynoates with s-Bu₂Cu(CN)Li₂, it is necessary to establish whether the reaction is proceeding by electron transfer or via a copper hydride species; in the first case, both hydrogen atoms incorporated into the product are transferred from the proton source during quenching, while in the latter case one hydrogen atom stems from the cuprate and one from the proton source. When the reaction of ester **1c** with s-Bu₂Cu(CN)Li₂ in diethyl ether is quenchend with CH₃COOD, it is found that two deuterium atoms are incorporated into the product; thus the reaction seems to occur via electron transfer. A possible reaction mechanism is outlined below.



Transfer of one electron from the cuprate to the envnoate **A** gives the radical anion **B** and a copper(II) species, which then transfers a second electron to **B**; alternatively, two electrons could be transferred in one step from the cuprate to **A**. The unstable copper(III) species thus formed decomposes rapidly to

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s-butylcopper and 2-methylbutyronitrile, whereas the dianionic species **C** (only one mesomeric formula drawn) is protonated at C-3 to give the 1,4-reduction product **D**, or at C-5 to give the 1,6-reduction product **E**. If the enyne carries a substitutent at C-3, the protonation at this center is disfavored, and the 1,6-reduction product **E** is formed exclusively (as observed experimentally for enynoate 1c). Further work is in progress in order to examine the scope and limitations of this reduction method.

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References and Notes

- 1) a) G.H. Posner, Org. React. 19 (1972) 1; Org. React. 22 (1975) 253.
 - b) Y. Yamamoto, Angew. Chem. 98 (1986) 945; Angew. Chem. Int. Ed. Engl. 25 (1986) 947.
 - c) B.H. Lipshutz, Synthesis 1987 325.
- 2) a) H.O. House, Acc. Chem. Res. 9 (1976) 59.
 - b) H.O. House, J.M. Wilkins, J. Org. Chem. 43 (1978) 2443
 - c) R.A.J. Smith, D.J. Hannah, Tetrahedron 35 (1979) 1183.
 - d) E.C. Ashby, D. Coleman, J. Org. Chem. 52 (1987) 4554.
 - e) R.A.J. Smith, A.S. Vellekoop, Tetrahedron 45 (1989) 517.
 - f) S.H. Bertz, G. Dabbagh, A.M. Mujsce, J. Am. Chem. Soc. 113 (1991) 631.
 - g) A. Alexakis, I. Marek, P. Mangeney, J.F. Normant, Tetrahedron 47 (1991) 1677.
- 3) A. Alexakis, D. Jachiet, J.F. Normant, Tetrahedron 42 (1986) 5607.
- 4) N. Krause, Chem. Ber. 123 (1990) 2173.
- 5) All compounds were obtained as oils after purification by column chromatography; 1,6-addition products **4** were isolated as 1:1 mixtures of diastereomers. Representative ¹H-NMR data (300 MHz): **2a**: $\delta = 1.27$ (t, 3H, J = 7.1 Hz, CO₂CH₂CH₃), 3.16 (m, 2H, 2-H), 4.18 (q, 2H, J = 7.1 Hz, CO₂CH₂), 5.72 (q, 1H, J = 6.7 Hz, 3-H), 6.22 (dt, 1H, J = 6.5/2.7 Hz, 5-H), 7.16-7.43 (m, 5H, phenyl-H). **3a**: $\delta = 1.28$ (t, 3H, J = 7.1 Hz, CO₂CH₂CH₃), 2.62 (m, 2H, 2-H/3-H), 2.72 (m, 2H, 2-H/3-H), 4.18 (q, 2H, J = 7.1 Hz, CO₂CH₂), 7.16-7.43 (m, 5H, phenyl-H). **4b**: $\delta = 0.84/0.86$ (2xt, 3H, 2xJ = 7.3 Hz, 8-H), 1.00 (d, 3H, J = 6.8 Hz, 6-CH₃), 1.03 (s, 9H, C(CH₃)₃), 1.26 (t, 3H, J = 7.1 Hz, CO₂CH₂CH₂), 1.40 (m, 2H, 7-H), 1.91 (m, 1H, 6-H), 2.96 (d, 2H, J = 7.1 Hz, 2-H), 4.14 (q, 2H, J = 7.1 Hz, CO₂CH₂), 5.27 (dt, 1H, J = 4.3/7.1 Hz, 3-H).
- 6) a) E.C. Ashby, J.J. Watkins, J. Am. Chem. Soc. 99 (1977) 5312.
 - b) B.H. Lipshutz, J.A. Kozlowski, R.S. Wilhelm, J. Org. Chem. 49 (1984) 3943.
 - c) B.H. Lipshutz, J.A. Kozlowski, C.M. Breneman, J. Am. Chem. Soc. 107 (1985) 3197.
 - d) S.H. Bertz, G. Dabbagh, J. Am. Chem. Soc. 110 (1988) 3668.
 - e) N. Krause, Tetrahedron Lett. 30 (1989) 5219.
- 7) E.C. Ashby, J.J. Lin, R. Kovar, J. Org. Chem. 41 (1976) 1939.
- 8) M.F. Semmelhack, R.D. Stauffer, A. Yamashita, J. Org. Chem. 42 (1977) 3180.
- 9) T. Tsuda, T. Hayashi, H. Satomi, T. Kawamoto, T. Saegusa, J. Org. Chem. 51 (1986) 537.
- 10) A.R. Daniewski, M.R. Uskokovic', Tetrahedron Lett. 31 (1990) 5599, and literature cited therein.
- 11) W.S. Mahoney, J.M. Stryker, J. Am. Chem. Soc. 111 (1989) 8818, and literature cited therein.
- 12) B.H. Lipshutz, C.S. Ung, S. Sengupta, Synlett 1989 64.
- 13) M. Narasida, I. Horibe, F. Watanabe, K. Takeda, J. Org. Chem. 54 (1989) 5308.

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