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Deconjugative Conversion of α-Alkynyl Esters to α,α-Disubstituted *β*-Alkynyl Esters

Salvatore D. Lepore* and Yuanjun He

Department of Chemistry, Florida Atlantic University, Boca Raton, Florida 33431-0991

slepore@fau.edu

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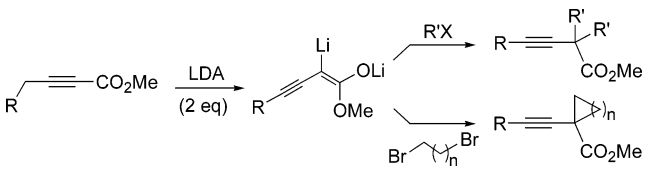
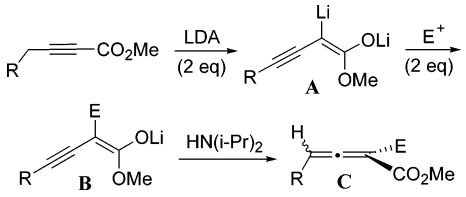


We report the development of a method for the conversion of a variety of conjugated α-alkynyl esters to α,α-disubstituted *β*-alkynylesters through the use of strong amide bases. Studies indicate that the second equivalent of base leads to the dianion intermediate. Optimal conditions included the use of 2 equiv of lithium diisopropylamide in THF with HMPA as the cosolvent followed by trapping with a variety of carbon electrophiles. Trapping with bis-electrophiles leads to spiro cycloalkane products.

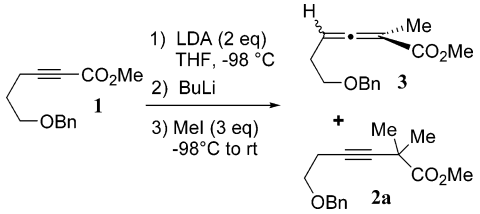
To date, the strong-base-promoted alkylative conversion of conjugated alkynyl esters to α,α-disubstituted *β*-alkynylesters has not been reported despite the potential utility of such a transformation. Although the analogous isomerization of α,*β*-unsaturated esters to the corresponding *β*,*γ*-unsaturated esters is well-known,[1] the use of similar procedures with α,*β*-unsaturated alkynyl esters has mainly led to allene products.[2] Using an electrochemical method, *β*,*γ*-unsaturated esters have been obtained from conjugated alkynyl esters.[2c] However, the approach suffers from issues of scalability and convenience.

Recently, we reported the development of an efficient method for the conversion of a variety of conjugated alkynyl esters to α-substituted conjugated allenyl esters (racemic) through the use of strong amide bases.[3] It was found that synthetically useful yields could only be achieved with the use of 2 equiv of lithium diisopropylamide (LDA). Our studies indicated that 2 equiv of LDA most likely led to the formation of dianion intermediate **A**.



Upon the addition of excess electrophile (TMS−Cl, MeI, and Bu_3Sn−Cl), we observed that allene **C** was the major product. The addition of a metal halide salt such as LiCl further increased the yield of the allene.[3]

TABLE 1. "Removal" of Diisopropylamine via BuLi Addition in the Methylation of Alkynyl Ester 1



equiv of BuLi	ratio of **3**:**2a**[a]	% yield of mixture
0	3.3:1.0	47
1	0.67:1.0	46
2	exclusively **2a**	41

[a] See ref 6.

Attempts to quench the alkylation reaction with deuterium sources (CD_3OD, D_2O, and DCl) failed to give deuterium incorporation. Thus, we hypothesized that the allene forms when enolate **B** abstracts a proton from the diisopropylamine present in the system as a result of LDA deprotonation of the substrate. The transfer of a proton from diisopropylamine to an enolate has been previously described to occur as part of a complex in which enolate and diisopropylamine are linked together by Li−N and hydrogen bonding.[4] Thus, the rapid intracomplex protonation precludes the intermolecular attack of excess electrophile, leading to monoalkylation product **C**.[5] We reasoned that if the diisopropylamine were deprotonated by a strong base such as butyllithium that it should lead to the dialkylated product. To test this hypothesis, alkynyl ester **1** was reacted with LDA (2 equiv) followed by varying equivalents of BuLi. This reaction mixture was then quenched with excess methyl iodide. We observed that two products were formed, allene **3** and deconjugated dimethyl ester **2a** (Table 1). With no added BuLi, the ratio of **3**:**2a** was 3.3,[6] and with 1 equiv of BuLi, the ratio was 0.67; with 2 equiv of BuLi, only product **2a** was observed. These BuLi addition experiments seem to indicate that the increased yield of deconjugation product is likely due to the removal of diisopropylamine via deprotonation.

We then examined alternative conditions to optimize the formation of the deconjugated alkyne product since

(1) For a recent example, see: Guha, S. K.; Shibayama, A.; Abe, D.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2003**, *32*, 778.

(2) (a) Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, *41*, 4249. (b) Shen, C. C.; Ainsworth, C. *Tetrahedron Lett.* **1979**, *20*, 89. (c) Tokuda, M.; Nishio, O. *J. Org. Chem.* **1985**, *50*, 1592.

(3) Lepore, S. D.; He, Y. J.; Damisse, P. *J. Org. Chem.* **2004**, *69*, 9171.

(4) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624 and references therein.

(5) (a) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396. (b) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M., Jr. *J. Org. Chem.* **1972**, *37*, 451.

(6) Since compounds **3** and **2a** are obtained as an inseparable mixture, their ratio was determined by comparing the area of the integrated signal of the allenyl methyl group in **3** with the area of the geminal dimethyl group in **2a** in an ^1H NMR spectrum of the mixture.

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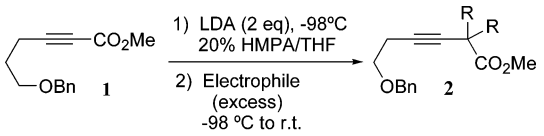
TABLE 2. Use of HMPA as a Decomplexing Agent to Give Exclusively Deconjugation Products 2



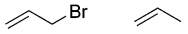
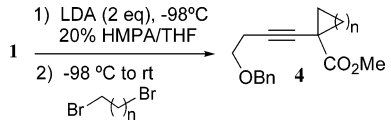
entry	electrophile	R	product	% isolated yield
1	CH_3I	CH_3	**2a**	65
2	HCl/Et_2O	H	**2b**	51
3	CH_3CH_2I	CH_3CH_2	**2c**	79
4	$PhCH_2Br$	$PhCH_2$	**2d**	76
5			**2e**	66

TABLE 3. Use of Symmetrical Dibromide Electrophiles and the HMPA Method to Give Spirocyclic Products 4



	n	% yield
4a	1	20
4b	2	0
4c	3	47
4d	4	51

the butyllithium approach suffered from poor overall yields. In our earlier study, we noted that the addition of metal halide salts increased the yield of allene **C** most likely by stabilizing lithium dianion complex **A** and thereby increasing the probability of intracomplex protonation. On the basis of this hypothesis, we would expect an increase in the formation of deconjugation product if the complex were destabilized.

Indeed, the use of a known decomplexing agent, HMPA,[7] as a 20% cosolvent with THF gave exclusive formation of the deconjugated product with a variety of electrophiles (Table 2). With methyl iodide, the isolated yield of deconjugated product **2a** was 65%, which is a substantial improvement over the BuLi technique (41%).

We also examined the bis-alkylation reaction with ditosylate and dibromide symmetrical electrophiles to give a spirocyclic product (Table 3). Synthetically useful yields were only obtained with 1,4-dibromobutane and 1,5-dibromopentane to give the five- and six-membered spirocyclic products **4c** and **4d**, respectively.[8]

In conclusion, we have identified conditions for the alkylative conversion of alkynyl esters to α,α-disubstituted β-alkynylesters in synthetically useful yields. Key factors in this conversion were the use of 2 equiv of LDA to form a dianion species and HMPA to destabilize complex formation, thereby preventing rapid intracomplex protonation, leading to the allene product.

Experimental Section

Representative Experimental Procedure. To a 25 mL round-bottom flask were added 6-benzyloxy-hex-2-ynoic acid methyl ester (139.6 mg, 0.60 mmol), THF (9.6 mL), and HMPA (2.4 mL). The solution was allowed to stir at −98 °C under nitrogen for 10 min followed by the dropwise addition of LDA (0.60 mL, 2 M, 1.20 mmol) while carefully maintaining the reaction temperature at −98 °C. Stirring was continued for an additional 30 min followed by the addition of neat MeI (0.3 mL, 4.8 mmol). The reaction mixture was maintained at −98 °C for 1 h and then allowed to warm to room temperature over the course of 8 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), followed by extraction with ether (10 mL) twice. The combined ether layers were washed with brine, dried over $MgSO_4$, and evaporated to leave the crude product, which was purified by column chromatography with silica gel eluting with 2% EtOAc/hexanes to obtain 102 mg (65%) of **6-benzyloxy-2,2-dimethyl-hex-3-ynoic acid methyl ester (2a)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H), 4.56 (s, 2H), 3.72 (s, 3H), 3.58 (t, J = 7.25 Hz, 2H), 2.51 (t, J = 7.0 Hz, 2H), 1.45 (s, 6H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 173.7, 138.4, 128.6 (2C), 127.8 (2C), 127.1, 83.6, 73.1, 68.8, 66.8, 52.9, 38.3, 27.7, 27.6, 20.4; HRMS calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1412

6-Benzyloxy-hex-3-ynoic Acid Methyl Ester (2b): ^{1}H NMR (400 MHz) δ 7.35−7.27 (m, 5H), 4.55 (s, 2H), 3.73 (s, 3H), 3.59 (t, J = 7.0 Hz, 2H), 3.27 (t, J = 2.4 Hz, 2H), 2.52 (tt, J = 7.0 Hz, 2.4 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 169.4, 138.3, 128.0 (2C), 127.8 (3C), 100.2, 80.7, 73.2, 69.1, 52.7, 32.0, 20.4; HRMS calcd for $C_{14}H_{16}O_3$ 232.1099, found 232.1099; $(M - H)^+$ 231.1021

6-Benzyloxy-2,2-diethyl-hex-3-ynoic Acid Methyl Ester (2c): ^{1}H NMR (400 MHz) δ 7.34−7.28 (m, 5H), 4.56 (s, 2H), 3.71 (s, 3H), 3.62 (t, J = 7.2 Hz, 2H), 2.57 (t, J = 7.0 Hz, 2H), 1.85−1.78 (m, 2H), 1.68−1.63 (m, 2H), 0.95 (t, J = 7.4 Hz, 6H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 174.0, 138.2, 128.4 (2C), 127.6 (3C), 80.8, 80.7, 72.9, 68.9, 52.3, 49.8, 32.3 (2C), 20.3, 9.8 (2C); HRMS calcd for $C_{19}H_{26}O_3$ 302.1882, found $(M - CH_3)^+$ 287.1648.

2,2-Dibenzyl-6-benzyloxy-hex-3-ynoic Acid Methyl Ester (2d): ^{1}H NMR (500 MHz) δ 7.40−7.25 (m, 15H), 4.56 (s, 2H), 3.58 (t, J = 7.2 Hz, 2H), 3.55 (s, 3H), 3.28 (d, J = 13.0 Hz, 2H), 2.97 (d, J = 13.0 Hz 2H), 2.55 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 138.1, 136.5 (2C), 130.3 (4C), 128.3 (3C), 127.8 (4C), 127.6 (2C), 126.8 (2C), 84.4, 79.8, 72.9, 68.5, 52.2, 51.6, 45.6 (2C), 20.2; HRMS calcd for $C_{28}H_{28}O_3$ 412.2083, found $(M - H)^+$ 411.1978.

2,2-Diallyl-6-benzyloxy-hex-3-ynoic Acid Methyl Ester (2e): ^{1}H NMR (500 MHz) δ 7.37−7.26 (m, 5H), 5.89−5.80 (m, 2H), 5.11−5.08 (m, 4H), 4.56 (s, 2H), 3.70 (s, 3H), 3.61 (t, J = 7.1 Hz, 2H), 2.56 (t, J = 7.1 Hz, 2H), 2.52 (m, 2H), 2.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 133.3 (3C), 128.4 (2C), 127.7 (3C), 118.4 (2C), 82.0, 72.9, 68.8, 52.4, 47.8, 42.8 (3C), 20.3; HRMS calcd for $C_{20}H_{24}O_3$ 312.1725, found $(M - H)^+$ 311.1616.

1-(4-Benzyloxy-but-1-ynyl)-cyclopentanecarboxylic Acid Methyl Ester (4c): ^{1}H NMR (400 MHz) δ 7.35−7.28 (m, 5H), 4.55 (s, 2H), 3.73 (s, 3H), 3.58 (t, J = 7.1 Hz, 2H), 2.52 (t, J = 7.1 Hz, 2H), 2.21−2.14 (m, 2H), 2.00−1.94 (m, 2H), 1.83−1.76 (m, 2H), 1.73−1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 138.2, 129.1, 128.4 (2C), 127.6 (2C), 83.0, 78.9, 72.9, 68.7, 52.7, 48.2, 39.2 (2C), 24.6 (2C), 20.3; HRMS calcd for $C_{18}H_{22}O_3$ 286.1569, found $(M + H)^+$ 287.1633.

1-(4-Benzyloxy-but-1-ynyl)-cyclohexane Carboxylic Acid Methyl Ester (4d): ^{1}H NMR (400 MHz) δ 7.37−7.27 (m, 5H), 4.56 (s, 2H), 3.72 (s, 3H), 3.61 (t, J = 7.1 Hz, 2H), 2.55 (t, J = 7.1 Hz, 2H), 1.88−1.81 (m, 2H), 1.76−1.63 (m, 4H), 1.56−1.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 138.2, 128.3 (2C), 127.6 (3C), 81.2, 81.0, 72.9, 68.8, 52.5, 43.6, 34.9, 34.8, 25.4, 22.3 (2C), 20.3; HRMS calcd for $C_{19}H_{24}O_3$ 300.1725, found $(M + H)^+$ 301.1805.

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(7) Piers, E.; Gavai. A. V. *J. Org. Chem.* **1990**, *55*, 2380.

(8) A small amount of the spirocyclopropane **4a** was obtained as an inseparable mixture with other unidentified products. The yield was estimated by NMR analysis.

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **2a**−**e** and compounds **4c** and **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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