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A New Method for the Preparation of Alkynes from Vinyl Triflates.

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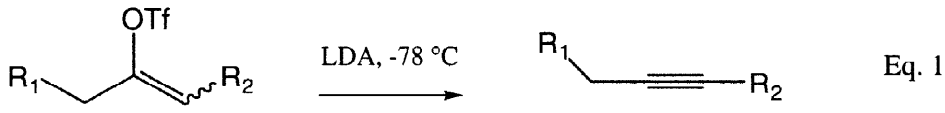
Abstract: Treatment of vinyl triflates with lithium diisopropylamide results in the selective formation of alkynes in moderate to high yields. © 1998 Elsevier Science Ltd. All rights reserved.

The importance of the alkyne moiety is evident by its appearance in biologically active compounds and its versatility as applied to functional group manipulations. Likewise, the many applications of this moiety in synthesis is matched by the number of methods available to prepare alkynes.[1] While methods to prepare alkynes are abundant, it is necessary to search for new methods which are more efficient and general. We would like to report that alkynes can be prepared in moderate to high yields from ketones via vinyl triflates (Eq. 1). This reaction was



Eq. 1

discovered during an attempt to increase the efficiency and selectivity of the conversion of enol phosphates to allenes developed in our group.[2] The elimination reaction of vinyl triflates to afford alkynes is not unprecedented. It has been demonstrated that benzyne can be prepared via the elimination reaction of an aryl triflate using lithium diisopropylamide.[3] In addition, pinacolone has been converted to 3,3-dimethyl-1-buten-2-yl triflate and in the presence of pyridine underwent an elimination of triflic acid to afford 3,3-dimethyl-1-butyne.[4] Finally, solvolysis of medium ring size vinyl triflates has been studied.[5] We would now like to report a more general method by which ketones can be converted to alkynes.

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Macrocyclic alkynes can be conveniently prepared from ketones by way of the vinyl triflate. For example, cyclododecanone and cyclopentadecanone are converted to their corresponding vinyl triflates via established protocols.[6] Upon treatment with freshly prepared lithium diisopropylamide (2 equiv) at -78 °C, the vinyl triflate underwent elimination affording high yields of cyclododecyne (entry 1) and cyclopentadecyne (entry 2) with very little contamination of the corresponding allenes.[7] For example, the cyclododecyne and cyclopentadecyne are obtained with an alkyne to allene ratio of 93 : 7 and 94 : 6, respectively. These elimination reactions are usually complete in less than two hours. These results are in contrast to our findings with the LDA-induced elimination of the enol phosphates of these macrocyclic ketones which provided allenes as the major elimination products.[2] The use of this method to prepare acyclic alkynes is also demonstrated by the conversion of 6-undecanone to its vinyl triflate. Treatment of this vinyl triflate with two equivalents of lithium diisopropylamide results in the formation of 5-undecyne (entry 3) in 80% yield (95 : 5, alkyne : allene).

Alternative bases were examined for the elimination of the vinyl triflate to afford 5-undecyne. Addition of two equivalents of n-BuLi resulted in a 52% yield (91 : 9, alkyne : allene); two equivalents of s-BuLi gave a 26% yield (95 : 5, alkyne : allene) and two equivalents of lithium hexamethyldisilylazide gave no reaction at room temperature after 2 days.

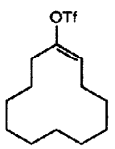
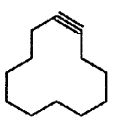
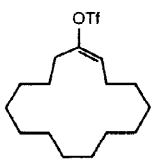
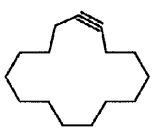
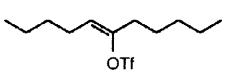
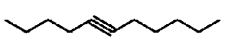
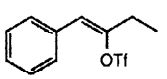
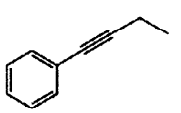
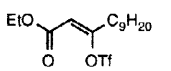
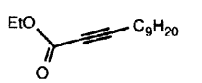
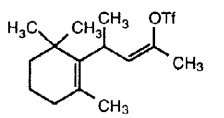
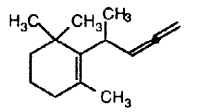
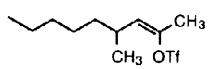
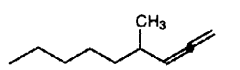
Phenyl alkynes can be prepared as shown by the conversion of 1-phenyl-2-butanone to the vinyl triflate. Subsequent treatment of the vinyl triflate to LDA (2 equiv) affords 1-phenyl-1-butyne as the only product in 68% yield (entry 4). β-Ketoesters can also be converted to alkynoate esters as shown by entry 5. Treatment of the vinyl triflate of ethyl-3-oxo-dodecanoate[8] to LDA (2 equiv) results in the formation of only ethyl-2-dodecynoate in 62% yield.

A limitation in this method was realized when the vinyl triflate, generated by trapping the conjugate addition product ($LiCu(CH_3)_2$) of β-ionone, was subjected to standard elimination conditions resulted in the formation of only the allene (entry 6). Two other bases (n-BuLi, KH) were tried in an attempt to bring about the formation of the alkyne with no success. We reasoned that the vinyl proton might be much more hindered as compared to the allylic proton and deprotonation at this position was not possible. However, when a less sterically encumbered system was investigated (entry 7), the results were the same. Based upon these two examples, it appears that any branching next to the vinyl proton leads to deprotonation of the less sterically hindered allylic position. Mixtures of *E* and *Z* isomers of the vinyl triflates for entries 1, 2, 3, 6, and 7 were subjected to the elimination conditions, so it would appear that the stereochemistry of the olefin does not play a part in this chemoselectivity.

General Procedure (Table I, Entry 1): To a solution of cyclododecanone (1.0 mmol) in 2 mL of THF was added freshly prepared lithium diisopropylamide (1.1 mmol) in 3 mL of THF at -78 °C. The resulting solution was stirred at -78 °C for 2 h at which time a solution of *N*-phenyltriflimide (1.07 mmol) in 2 mL of THF was added and the reaction was allowed to warm to 0 °C. The reaction was maintained at this temperature until completion, as observed by TLC. The workup consisted of filtering the reaction solution through a plug of silica gel using ether as eluent. The solvent was removed via rotary evaporation and the residue was purified via flash chromatography on silica gel (eluting with hexanes) furnishing an 85% yield of the corresponding vinyl triflate. To a solution of this vinyl triflate (0.35 mmol) in 1 mL of THF at -78 °C was added a solution of lithium diisopropylamide (0.70 mmol) in 1 mL of THF over 5 min. The LDA solution was prepared at 0 °C then cooled to -78 °C prior to cannulation. The reaction mixture was stirred at -78 °C for 2 h then poured onto pentane/water.

The aqueous phase was extracted with pentane (3 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. An HPLC trace of the crude product shows a 93 : 7 ratio of alkyne to allene. The selectivity was determined by the HPLC method using a silica column with hexanes as the eluent. Purification of the resulting oil by flash chromatography on silica gel (eluting with pentane) furnished a 95% yield of cyclododecyne.

TABLE I

Entry	Vinyl Triflate	Product	Yield
1	 *E* : *Z*, 1 : 10		95%
2	 *E* : *Z*, 1 : 2		87%
3	 *E* : *Z*, 1 : 1.2		80%
4	 single isomer		69%
5	 single isomer		62%
6	 *E* : *Z*, 8 : 1		65%
7	 *E* : *Z*, 5 : 1		43%

In conclusion, conjugated alkynoate esters (entry 5), macrocyclic (entries 1 and 2), alicyclic (entry 3), and aryl (entry 4) alkynes can be prepared from ketones in moderate to high yields by an elimination reaction of the intermediate vinyl triflate. Some limitations in this method have been realized as evidenced by entries 6 and 7. Branching at the α-position of the vinyl proton to be abstracted, leads to deprotonation at the less hindered allylic position giving rise to the allene instead of alkyne.

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7. All new compounds reported herein exhibit satisfactory spectral data (IR, ^{1}H NMR, ^{13}C NMR, GC/MS). Representative spectral data: ***E,Z*-5-undecenyl-6-trifluoromethylsulfonate**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.49 (t, *J* = 7.9 Hz, 1H), 5.21 (t, *J* = 7.4 Hz, 1H), 2.29-2.45 (m, 4H), 2.01-2.19 (m, 4H), 1.22-1.59 (m, 20H), 0.82-1.02 (m, 12H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 122.0, 121.1, 121.0, 120.9, 116.3, 116.1, 33.5, 31.3, 31.0, 31.0, 30.9, 29.7, 26.4, 26.4, 26.0, 26.0, 25.5, 22.3, 22.2, 22.1, 13.9, 13.8, 13.8; IR (neat) 2961, 2934, 2864, 1687, 1468, 1415 cm^{-1}; MS (GC/MS) *m/z* 302 (M^+). **5-undecyne:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.13 (m, 4H), 1.41 (m, 10H), 0.89 (m. 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 80.3, 80.2, 31.4, 31.2, 28.9, 22.3, 22.0, 18.8, 18.5, 14.1, 13.7; IR (neat) 2932, 2861, 2364, 1654, 1560, 1458; MS (GC/MS) *m/z* 152 (M^+). **ethyl 2-dodecenyloate-trifluoromethanesulfonate** ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.73 (s, 1H), 4.22 (q, *J* = 8.1 Hz, 2H), 2.36 (t, *J* = 8.1, 2H), 1.55 (m, 2H), 1.27 (m, 15H), 0.87 (t, *J* = 6.7Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 162.0, 159.1, 111.8, 61.3, 34.5, 31.9, 29.4, 29.3, 29.2, 28.7, 25.9, 22.7, 14.2, 14.1; IR (neat) 2931, 2864, 1734, 1684, 1654, 1430, 1209, 1143, 920; MS (GC/MS) *m/z* 375 (M^+ +1) 329, 277, 262. **ethyl 2-decynoate:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.2 Hz, 2H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.53-1.61 (m, 2H), 1.19-1.41 (m, 15H), 0.86 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 154.0, 89.6, 73.2, 61.8, 31.9, 29.4, 29.3, 29.1, 28.9, 27.6, 22.7, 18.7, 14.2, 14.1, ; IR (neat) 2927, 2856, 2344, 2236, 1718, 1559, 1540, 1457, 1251, 1075 cm^{-1}; MS (GC/MS) *m/z* 225 (M^+ +1). ***E,Z*-cyclopentadecenyl trifluoromethylsulfonate:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.51 (t, *J* = 7.9 Hz, 1H), 5.22 (t, *J* = 6.9 Hz, 1.6H), 2.41-2.35 (m, 4H), 2.24 (q, *J* = 6.0 Hz, 2H), 2.07 (q, *J* = 7.0 Hz, 2H), 1.6-1.15 (m, 44H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 150.5, 149.2, 122.6, 122.5, 118.5 (q, *J* = 319 Hz, CF_3), 29.3, 28.0, 27.9, 27.4, 27.2, 27.1, 27.1, 27.0, 26.9, 26.8, 26.8, 26.7, 26.6, 26.3, 26.2, 26.0, 25.6, 25.2, 25.0, 25.0; IR (neat) 2930, 2858, 1413, 1208, 1142, 899 cm^{-1}; MS (GC/MS)*m/z* 356 (M^+). **cyclopentadecyne:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.26–2.12 (m, 4H), 1.50-1.21 (m, 22H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 80.5, 28.4, 27.1, 27.0, 26.9, 26.7, 25.1, 18.4; IR (neat) 2927, 2855, 1458, 1350, 1329 cm^{-1}; MS (GC/MS) *m/z* 232 (M^+).
8. This triflate was prepared by the addition of 1 equivalent of NaH to the ketoester, followed by the addition of 1.1 equivalents of *N*-phenyltriflimide.