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Synthesis of Functionalized α,α-Disubstituted *β*-Alkynyl Esters from Allenoates through an Alkynylenolate Intermediate

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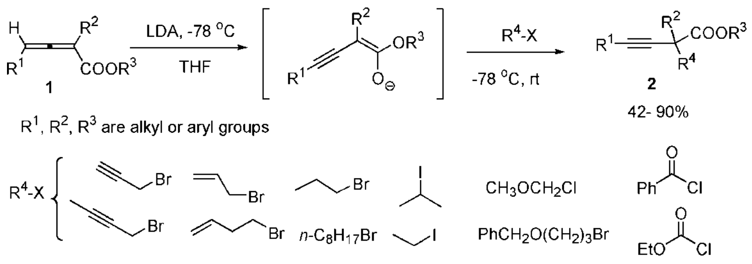
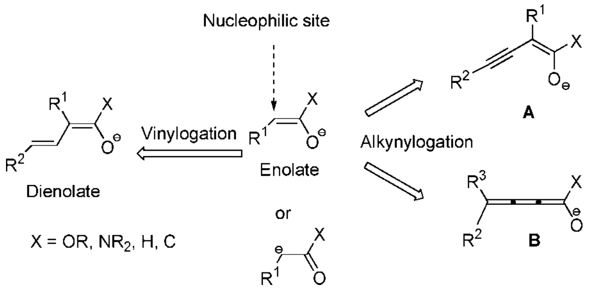
ABSTRACT



Highly substituted α,α-disubstituted *β*-alkynyl esters are readily prepared from allenyl esters and either alkyl halide, acid chloride, or alkyl chloroformate, mediated by an amide base. This highly efficient and mild process tolerates various functional groups and provides α,α-disubstituted *β*-alkynyl esters in good to excellent yields. This method is especially suitable for the synthesis of 1,*n*-enynes or 1,*n*-diynes (*n* > 4). Electrophilic cyclization of 1,5-enyne gives a highly functionalized *γ*-iodolactone, whereas its platinum-catalyzed cycloisomerization affords 1,3-cyclohexadiene.

Enolates are used pervasively throughout organic synthesis. A comprehensive survey of GMP bulk reactions run in a research facility between 1985 and 2002 showed that 68% of all C−C bond formations are carbanion based, and 44% of these involved enolates.[1] If a double or triple bond is appended to the enolate precursor through conjugation, it gives rise to the so-called extended enolates (Scheme 1). Among these, the chemistry of dienolates has received the most attention (Scheme 1, left).[2−4] A highly attractive alternative, but as yet much less explored, is the reaction of an enolate conjugated with a triple bond or allene moiety (**A** or **B** in Scheme 1, right).[5] Because there are two nucleophilic centers in an extended enolate, regioselectivity

Scheme 1. Alkynylogation and Vinylogation As Extensions of Enolates



[†] B. Xu and G.B. Hammond share senior authorship.

(1) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Process Res. Dev.* **2005**, *9*, 253–258.

(2) For a selected review, see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972.

(3) Denmark, S. E.; Heemstra, J. R,.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.

(4) (a) Kalesse, M. *Natural Products Synthesis II Targets, Methods, Concepts*, 2005; Vol. 244. (b) For an early review on the ambiphilic nature of allenyl enolates, see: Frederick, M. A.; Hulce, M. *Tetrahedron* **1997**, *53*, 10197–10227.

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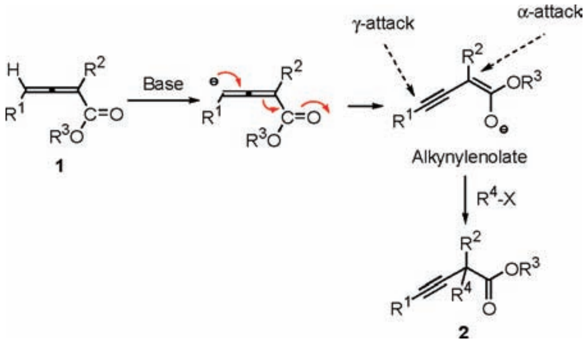
is a major concern in the reaction of extended enolates with electrophiles.

Recently, we reported a thermodynamically favored aldol reaction of propargylic or allenyl esters, through a common alkynylenolate intermediate (**A** in Scheme 1), which led to the regioselective synthesis of carbinol allenoates (exclusive γ-selectivity).[6] As an ongoing exploration of this chemistry, herein we report the reaction of alkynylenolate, prepared from **1**, with other electrophiles like alkyl halides or acid chlorides, to give exclusively the α-product **2** (Scheme 2).

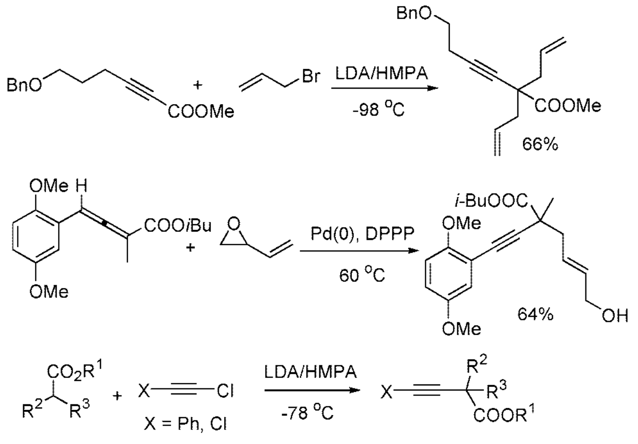
Scheme 2. Allenoates Are Precursors of Alkynylenolates



This discovery has led to a one-step synthesis of highly functionalized α,α-disubstituted β-alkynyl esters **2** from the readily available allenoate **1**.

Functionalized α,α-disubstituted β-alkynyl esters **2** are important synthetic synthons and targets.[7,8] There are several reported methods to make them, but most of them have limited scope. For example, Lepore and co-workers reported a method for the conversion of conjugated α-alkynyl esters to α,α-disubstituted (i.e., $R^2{=}R^4$ in **2**) β-alkynylesters using 2 equiv of LDA/HMPA at −98 °C (Scheme 3, top).[9]

Scheme 3. Literature Methods for the Preparation of α,α-Disubstituted β-Alkynyl Esters

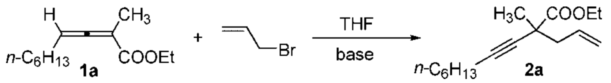


Alper and Nanayakkara obtained **2** through the reaction of allenoates with vinyl oxiranes in the presence of a palladium catalyst (Scheme 3, middle).[10] Another method to make **2** is by coupling an alkynyl halide with an α,α-disubstituted ester (Scheme 3, bottom), but only a few active alkynyl halides can be used (X = Ph, Cl).[11−13] **2** can also be prepared from sulfonylallenes but only in an intramolecular fashion.[14]

We have demonstrated in the past that both allenoates and propargylic esters can be suitable precursors of an alkynylenolate anion.[6] If allenoate **1** is treated with a strong enough base, the deprotonation of the γ-hydrogen atom of **1** will occur, furnishing the alkynylenolate anion (Scheme 2). Because allenoates can be prepared easily using a standard methodology,[15,16] in this report we have only used allenoates **1** as precursors of alkynylenolates and investigated their reactions with alkyl halides or acid chlorides.

We began by examining the influence of different bases and temperatures in the reaction of allenoate **1a** with allyl bromide. The results are summarized in Table 1.

Table 1. Optimization of Synthesis of α,α-Disubstituted β-Alkynyl Esters[a]



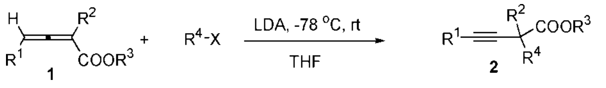
entry	base/equiv	temp	yield[b]
1	TBAF/2	0 °C, rt	no reaction
2	DBU/1.5	0 °C, rt	no reaction
3	*t*-BuOK/1.5	0 °C, rt	72%
4	LDA(HMPA)/1.5(3)	−78 °C, rt	71%
5	LDA/1.5	−78 °C, rt	88%

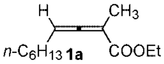
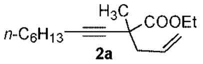
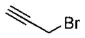
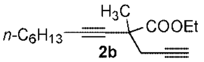
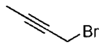
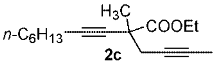
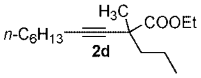
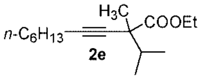
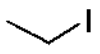
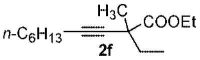
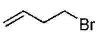
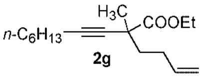
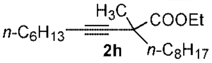
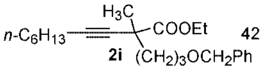
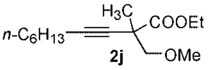
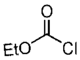
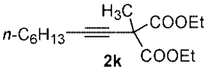
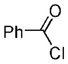
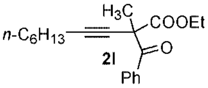
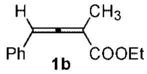
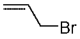
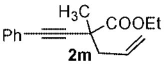
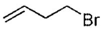
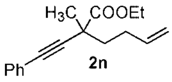
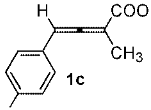
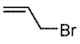
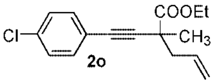
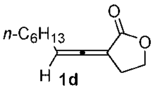
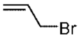
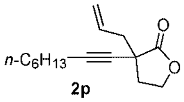
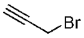
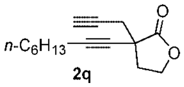
[a] Reaction condition: allenoate (0.5 mmol), allyl bromide (0.75 mmol), LDA (0.75 mmol), THF (2 mL). [b] Yields of isolated compound. LDA = lithium diisopropyl amide, DBU = 1,8-diazabicyclo[5,4,0]undec-7-ene, HMPA = hexamethyl phosphoramide.

When we used TBAF—the base of choice in our reported alkynylogous aldol reaction (reaction of an alkynylenolate with an aldehyde)[6]—no reaction occurred. An organic base like DBU did not mediate this reaction either. We believe that this is due to the fact that DBU and TBAF are nucleophilic bases and may displace allyl bromide, so we used a hindered, less nucleophilic base. To our delight, the reaction proceeded in excellent yield (88%) using LDA, one of the most frequently used amide bases in synthetic organic chemistry (Table 1, entry 5). By using LDA in the presence of HMPA, a common combination in enolate chemistry, only a moderate yield (71%) was obtained (Table 1, entry 4). Similarly, in the presence of *t*-BuOK, we also got a similar lower yield (72%) (Table 1, entry 3).

Next, we investigated the scope of this reaction by examining various types of halides and substituted allenoates under the optimized conditions found above (Table 2). These reactions proceeded smoothly, and α,α-disubstituted β-alkynyl esters **2** were obtained in good to excellent yields. Reaction of **1a** with reactive alkyl halides like allyl bromide or propargyl bromide gave better yields (Table 2, entries

Table 2. Synthesis of α,α-Disubstituted *β*-Alkynyl Esters[a]



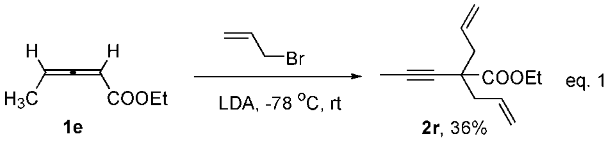
entry	1	R4-X	2	yield[b]
1	 1a		 2a	88%
2	1a		 2b	78%
3	1a		 2c	78%
4	1a		 2d	54%
5	1a		 2e	60%
6	1a		 2f	74%
7	1a		 2g	81%
8	1a	n-C_8H_{17}Br	 2h	67%
9	1a	$PhCH_2O(CH_2)_3Br$	 2i	42%
10	1a	CH_3OCH_2Cl (MOMCl)	 2j	90%
11	1a		 2k	66%
12	1a		 2l	64%
13	 1b		 2m	79%
14	1b		 2n	60%
15	 1c		 2o	72%
16	 1d		 2p	42%
17	1d		 2q	40%

[a] Reaction condition: allenoate **1** (0.5 mmol), R^4−X (0.75 mmol), LDA (0.75 mmol). [b] Yields of isolated compound (LDA = lithium diisopropyl amide).

1−3) than with unreactive alkyl halides (Table 2, entries 4−9). Reaction of an unconventional alkyl halide like MOMCl gave an excellent yield of **2j** (Table 2, entry 10). The reaction with a secondary alkyl halide proceeded well (Table 2, entry 5) and so did the reactions with acid chloride and alkyl chloroformate (Table 2, entries 11−12). Reactions of aryl-substituted allenoates, such as **1b** and **1c**, worked nicely (Table 2, entries 13−15). However, the yields for the reaction of **1d** with allyl bromide or propargyl bromide were modest, perhaps due to the instability of **1d**[17] (Table 2, entries 16 and 17).

The cycloisomerization of 1,*n*-enynes and 1,*n*-diynes is currently a highly competititive field in organic synthetic chemistry, with numerous applications appearing increasingly often in the literature.[18] Our method is especially suitable for the synthesis of hitherto inaccessible functionalized 1,*n*-enynes and 1,*n*-diynes ($n > 4$). For example, 1,5-enynes (**2a**, **2m**, **2o**, **2p**), 1,6-enynes (**2 g, 2n**), and 1,5-diynes (**2b**, **2c**, **2q**) can be prepared in high yields in a single step.

We have explored the reaction of α,*γ*-unsubstituted allenoate (**1e**) with allyl bromide; in this case, the reaction could not be stopped to give the monosubstituted product. Instead, it gave the disubstituted product **2r** (eq 1).



Scheme 4 illustrates our proposed mechanism for the formation of **2r**. First, deprotonation of **1e** gives alkynylenolate **A**, which then reacts with allyl bromide to afford **3**.

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(5) (a) Blagoev, B.; Jordanov, B.; Ivanoff, D. *Bull. Soc. Chim. Fr.* **1967**, 4657–4659. (b) Himbert, G. *J. Chem. Res. (S)* **1979**, 88–89. (c) Petasis, N. A.; Teets, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 10328–10334. (d) Lepore, S. D.; He, Y.; Damisse, P. *J. Org. Chem.* **2004**, *69*, 9171–9175. (e) Denichoux, A.; Ferreira, F.; Chemla, F. *Org. Lett.* **2004**, *6*, 3509–3512.

(6) Xu, B.; Hammond, G. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 689–692.

(7) Diederich, F.; Stang, P.; Tykwinski, R. R. *Acetylene chemistry: chemistry, biology, and material science*; Wiley-VCH: Weinheim, 2005, p 59.

(8) Just, Z. W.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 2662–2667.

(9) Lepore, S. D.; He, Y. *J. Org. Chem.* **2005**, *70*, 4546–4548.

(10) Nanayakkara, P.; Alper, H. *J. Org. Chem.* **2004**, *69*, 4686–4691.

(11) Kende, A. S.; Fludzinski, P.; Hill, J. H. *J. Am. Chem. Soc.* **1984**, *106*, 3551–62.

(12) Lin, G.-Y.; Yang, C.-Y.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 6753–6757.

(13) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705–9710.

(14) For a recent example of alkynyl-substituted cyclization products from sulfonylallene derivatives by base treatment, see: Kitagaki, S.; Teramoto, S.; Mukai, C. *Org. Lett.* **2007**, *9*, 2549–2552, and references cited therein.

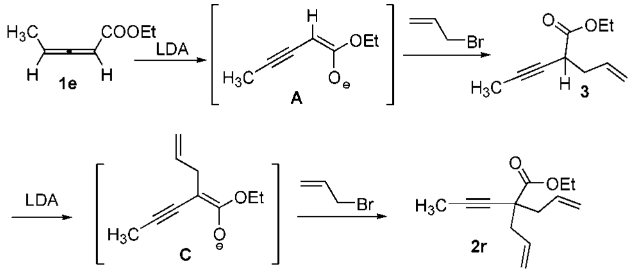
(15) Lang, R. W.; Hansen, H.-J. *Org. Synth., Coll. Vol. 7* **1990**, 232.

(16) For selected recent papers on allenoates, see:(a) Elsner, P.; Bernardi, L.; Dela Salla, G.; Overgaard, J.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 4897–4905. (b) Singh, L.; Ishar, M. P. S.; Elango, M.; Subramaniam, V.; Gupta, V.; Kanwal, P. *J. Org. Chem.* **2008**, *73*, 2224–2233. (c) Shi, M.; Tang, X.-Y.; Yang, Y.-H. *Org. Lett.* **2007**, *9*, 4017–4020. (d) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988–10989. (e) Li, C.-Y.; Sun, X.-L.; Jing, Q.; Tang, Y. *Chem. Commun.* **2006**, 2980–2982. (f) Klein, A.; Miesch, M. *Synthesis* **2006**, 2613–2617.

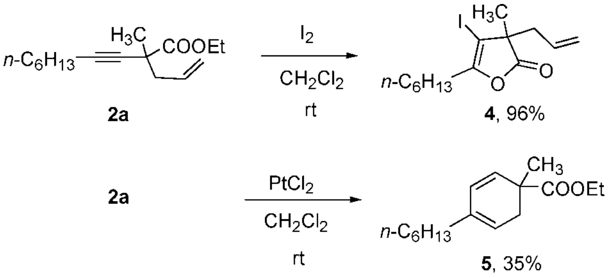
(17) **1d** decomposes at room temperature within one day.

(18) For a recent review: Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268−4315 and references cited therein.

Scheme 4. Proposed Mechanism for the Formation of **2r**



Scheme 5. Synthetic Transformations of **2a**



Intermediate **3** may isomerize to the corresponding allene, but in basic media, deprotonation of **3**, or its corresponding allene, will furnish alkynylenolate **C**. Finally, the reaction of **C** with another molecule of allyl bromide affords **2r**.

With a very easy and high-yielding synthesis of α,α-disubstituted β-alkynyl esters **2**, we decided to explore their synthetic potential (Scheme 5). Electrophilic cyclization of 3-alkynoate esters has been reported by Larock and co-workers very recently.[8] Using similar conditions, 1,5-enyne **2a** undergoes a highly efficient and mild I_2-mediated electrophilic cyclization[7] to afford the functionalized γ-lactone **4** in excellent yield. Furthermore, **2a** cycloisomerizes readily, at ambient temperature, using $PtCl_2$ as catalyst, to afford 1,3-cyclohexadiene **5** (Scheme 5, yield not optimized).[13]

In summary, we have developed a one-step, extremely efficient approach to various highly functionalized, substituted α,α-disubstituted β-alkynyl esters **2**, through the reaction of allenyl esters with various types of organic halides. These reactions are run under mild conditions and tolerate a number of functional groups. The broader implications of this reaction in organic synthesis, including its asymmetric variant, are currently under investigation.

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Supporting Information Available: Experimental procedures and NMR spectra for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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