ORGANIC LETTERS

2008
Vol. 10, No. 24
5589−5591

Highly Regioselective Fluorination and Iodination of Alkynyl Enolates

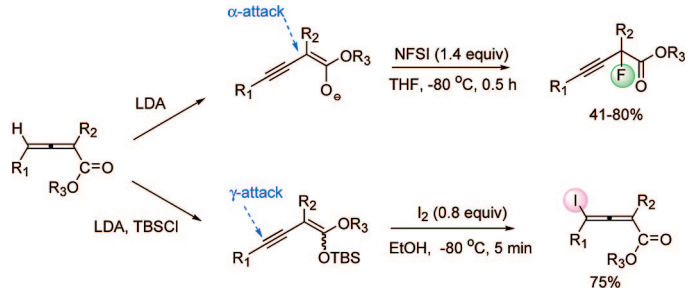
Han Yang, Bo Xu, and Gerald B. Hammond*

Department of Chemistry, University of Louisville, Louisville, Kentucky 40292

gb.hammond@louisville.edu

Received October 23, 2008

ABSTRACT



A simple yet efficient approach to various functionalized quaternary α-alkynyl α-fluoro esters and γ-iodoallenoates from readily available allenoates through an alkynyl enolate intermediate generated by LDA is presented. Reaction of this alkynyl enolate with NFSI gives the α-product (α-alkynyl-α-fluoro ester), whereas the reaction of the silyl ether of alkynyl enolate with I_2 gives solely the γ-product (iodoallenoate).

The regioselective synthesis of substituted γ-iodoallenoates or α-fluoropropargyl esters from a common, readily available precursor is a sought after strategy because the resulting products are either useful synthons or possess important biological properties. An example of the former is the recent surge of interest in the synthetic applications of γ-iodoallenes.[1] Examples of the latter are the extensive therapeutical ramifications of α-fluoro esters,[2] used in the synthesis of fluorinated amino acids,[3] anticancer reagents,[4] antiviral agents,[5] antibiotics,[6] and other pharmaceutically attractive molecules.[7] Because of the versatility of the triple bond,[8] an alkyne-substituted α-fluoro ester would enhance the range of α-fluoro carboxylic acids and derivatives. But unlike their nonfluorine counterpart, which is easy to obtain and has found numerous applications in synthesis,[9] the synthesis of α-alkyne-substituted α-fluoro esters[10] has a limited scope and utilizes $CHCl_2F$, an ozone-depleting reagent.

Recently, we reported the regioselective synthesis of carbinol allenoates,[11] α,α-disubstituted α-alkynyl esters,[12]

(1) (a) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440–1452. (b) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117–2120. (c) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500–10501. (d) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081–3084. (e) Ohno, H.; Ando, K.; Hamaguchi, H.; Takeoka, Y.; Tanaka, T. *J. Am. Chem. Soc.* **2002**, *124*, 15255–15266. (f) Xia, Y.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6940–6941.

(2) (a) Bellezza, F.; Cipiciani, A.; Ricci, G.; Ruzziconi, R. *Tetrahedron* **2005**, *61*, 8005–8012. (b) Fujisawa, H.; Fujiwara, T.; Takeuchi, Y.; Omata, K. *Chem. Pharm. Bull.* **2005**, *53*, 524–528. (c) Polla, M. O.; Tottie, L.; Norden, C.; Linschoten, M.; Musil, D.; Trumpp-Kallmeyer, S.; Aukrust, I. R.; Ringom, R.; Holm, K. H.; Neset, S. M.; Sandberg, M.; Thurmond, J.; Yu, P.; Hategan, G.; Anderson, H. *Bioorg. Med. Chem.* **2004**, *12*, 1151–1175.

(3) Edmonds, M. K.; Graichen, F. H. M.; Gardiner, J.; Abell, A. D. *Org. Lett.* **2008**, *10*, 885–887.

(4) (a) Burchardt, A.; Takahashi, T.; Takeuchi, Y.; Haufe, G. *J. Org. Chem.* **2001**, *66*, 2078–2084. (b) Haufe, G.; Burchardt, A. *Eur. J. Org. Chem.* **2001**, *450*, 1–4507.

(5) Lee, K.; Choi, Y.; Hong, J. H.; Schinazi, R. F.; Chu, C. K. *Nucleosides, Nucleotides Nucleic Acids* **1999**, *18*, 537–540.

(6) Ihara, M.; Satoh, K.; Ishida, Y.; Taniguchi, N.; Tokunaga, Y.; Takemura, M.; Fukumoto, K. *Heterocycles* **1996**, *42*, 437–443.

(7) Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 164–168.

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

(9) (a) Just, Z. W.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 2662–2667. (b) Lin, G.-Y.; Yang, C.-Y.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 6753–6757. (c) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705–9710. (d) Choi, K. S.; Akiyama, I.; Hoshino, M.; Nakayama, J. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 623–9.

(10) Xu, B.; Hammond, G. B. *J. Org. Chem.* **2006**, *71*, 3518–3521.

10.1021/ol802451e CCC: $40.75
Published on Web 11/18/2008

Scheme 1. Reaction Paths of an Alkynyl Enolate with a Halogenation Reagent

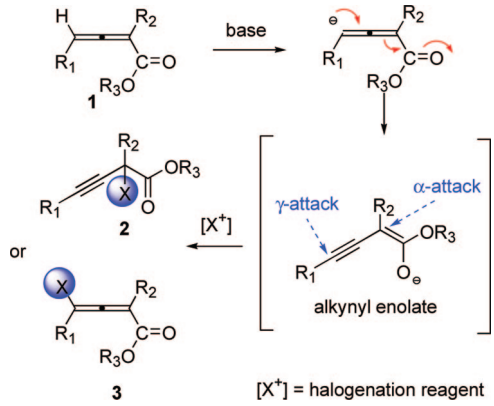
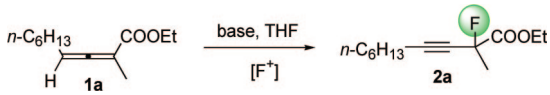


Table 1. Fluorination of Allenoate **1a**

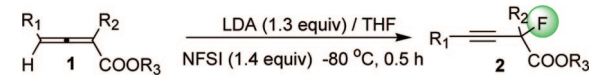


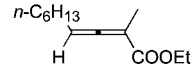
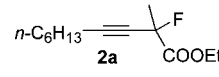
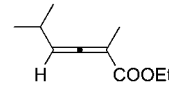
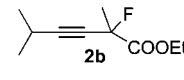
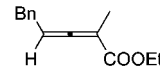
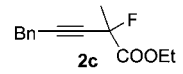
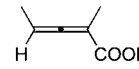
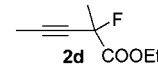
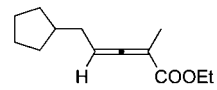
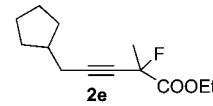
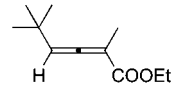
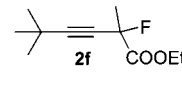
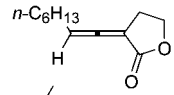
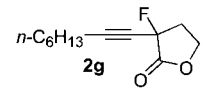
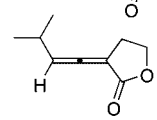
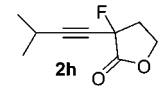
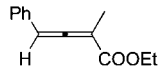
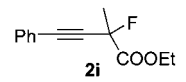
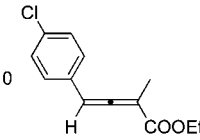
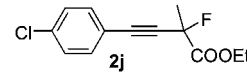
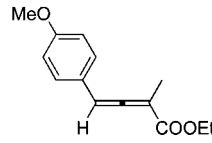
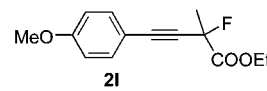
entry	base (equiv)	[F+] (equiv)	T (°C)/time (h)	yield[a] (%)
1	LDA (1.3)	NFSI (1.4)	−50 to rt/3	complex
2	LDA (1.3)	NFSI (1.4)	−80/0.5	80
3	NaHMDS (1.3)	NFSI (1.4)	−80/0.5	61
4	LiHMDS (1.3)	NFSI (1.4)	−80/0.5	no reaction
5	LDA (1.3)	Selectfluor (1.4)	−80/0.5	no reaction

[a] Isolated yields.

and 2-alkynyl-substituted glutaric acid derivatives.[13] Because an alkynyl enolate anion could, in theory, react with an electrophilic halide source to produce regioisomers **2** or **3**, through either an α- or γ-attack, the thrust of this work was to make this reaction regioselective. We are now pleased to report that when a readily available allenoate **1** was deprotonated with LDA and trapped with a fluorinating agent, it reacted exclusively at the α-carbon forming α-alkynyl-α-fluoro ester **2** (Scheme 1). Conversely, iodination at the γ-carbon of allenoate **1**—a hitherto difficult feat[1]—was readily accomplished when the silyl ketene acetal **4** reacted with I_2. We first investigated the fluorination of alkynyl enolates derived from allenoate **1** (Table 1) because allenoates are widely used in synthesis,[14] and can be prepared easily using standard methodologies.[15] Upon treatment of allenoate **1a** with LDA at −50 °C, followed by addition of a solution of NFSI in THF, then the reaction mixture was warmed to room temperature, it was observed that the consumption of **1a** was accompanied by the appearance of a complex mixture (Table 1, entry 1). When the reaction was conducted at lower temperature (−80 °C) for shorter times, and quenched also at low temperature, the desired **2a** was isolated in 80% yield (Table 1, entry 2). More importantly, no traces of the regiosomeric fluoroallene were found.

Table 2. Regioselective Fluorination of Allenoates



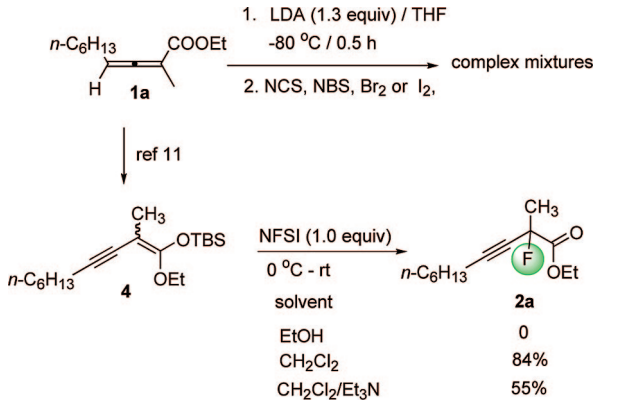
entry	1	2	yield %[a]
1			80
2			39
3			21
4			56
5[b]			55
6[c]			60
7			72
8			49
9			59
10			43
11			41

[a] Isolated yields. [b] LDA (1.5 equiv), NFSI (1.5 equiv), −80 °C for 40 min, then −40 °C for 1 h. [c] −80 °C for 0.5 h, then 0 °C for 0.5 h.

Use of other amide bases like NaHDMS and LiHMDS gave less satisfactory results (Table 1, entries 3 and 4). Selectfluor was not an efficient fluorination reagent under our reaction conditions (Table 1, entry 5).

Next, we examined the scope of this regioselective fluorination. The results are shown in Table 2. The yields in some entries are moderate due to the volatile nature of products (Table 2, entries 2, 4, and 8), but both aryl- and alkyl-substituted allenoates give good to very good yields. The steric nature of substituents on the allenoate **1** had an

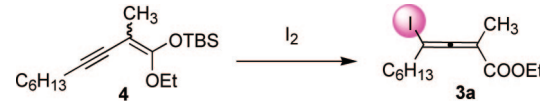
Scheme 2. Fluorination of **1** through the Intermediacy of Silyl Ketene Acetal **4**



effect on the reaction rate; for example, allenoates with a bulky R^1 group needed an excess of NFSI and higher temperature/longer times to complete the reaction (Table 2, entries 5 and 6). Using similar conditions with other common halogenation reagents like NCS, NBS, Br_2, or I_2 did not give the desired products (Scheme 2, top). This may due to the unstable nature of the propargylic or allenylic products under the strong basic conditions used.

To avoid the use of a strong base, we switched to using the silyl alkynyl ketene acetal **4**[11] and investigated its reactivity toward halogenation. The reaction with NFSI (Scheme 2, bottom) using dichloromethane produced **2a** in 84% yield. This reaction could be regarded as an alternative way to synthesize α-alkynyl-α-fluoro ester **2**. Then we examined the reaction of **4** with other halogenation reagents. With NBS, NCS, and Br_2, this reaction did not give a clean transformation but the reaction of **4** with I_2 was very successful (Table 3).

Table 3. Iodination of Silyl Alkynyl Ketene Acetal **4**



entry	I_2 (equiv)	solvent	T (°C)	time	yield (%)[a]
1	1.2	DCM	0	1.5 h	complex reaction
2	0.40	DCM	0	1.5 h	complex reaction
3	0.95	DCM	−80	10 min	unknown allene
4	0.95	MeOH	−80	5 min	47
5	0.95	EtOH	−80	5 min	50
6	0.95	THF	−80	5 min	complex mixture
7	0.8	EtOH	−80	5 min	75
8	0.8	DCM	−80	5 min	70
9	0.8	THF	−80	5 min	63

[a] Isolated yields.

Because the iodoallene **3a** is relatively unstable, longer reaction times and high temperatures promoted the formation of byproduct (Table 3, entries 1−6). At −80 °C, EtOH was found to be the best solvent, compared with DCM, THF, or MeOH. Using less than stoichiometric amounts of iodine boosted the yield because the product **3a** may react with excess amount of I_2 creating a complex mixture of products.

The opposite behavior of the lithium alkynylenolate vis à vis the alkynyl silyl ketene acetal—in terms of regioselectivity toward NFSI and I_2—could be accounted for by the higher electron density at the α-position of the former.[11]

In summary, we have developed a simple, practical, and regioselective approach to various highly functionalized α-alkynyl-α-fluoro ester and γ-iodoallenoates starting from readily available allenoates **1**. An expansion of this reaction to other venues of organic chemistry is currently under investigation.

Acknowledgment. We are grateful to the National Science Foundation for financial support (CHE-0809683).

Supporting Information Available: Experimental procedures and NMR spectra for **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802451E

(11) Xu, B.; Hammond, G. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 689–692.
(12) Wang, W.; Xu, B.; Hammond, G. B. *Org. Lett.* **2008**, *10*, 3713–3716.
(13) Liu, L.-P.; Xu, B.; Hammond, G. B. *Org. Lett.* **2008**, *10*, 3887–3890.
(14) Selected references on allenoates: (a) Lu, Z.; Chai, G.; Zhang, X.; Ma, S. *Org. Lett.* **2008**, *10*, 3517–3520. (b) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. *Chem.—Eur. J.* **2008**, *14*, 4361–4373. (c) Huang, X.; Sha, F. *J. Org. Chem.* **2008**, *73*, 1173–1175. (d) Elsner, P.; Bernardi, L.; Salla, G. D.; Overgaard, J.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 4897–4905. (e) Creech, G. S.; Kwon, O. *Org. Lett.* **2008**, *10*, 429–432. (f) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470–1. (g) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632–12633. (h) Lu, Z.; Chai, G.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 14546–14547. (i) Jiang, X.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 11600–11607. (j) Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431–7433.
(15) Lang, R. W. Hansen, H.-J. *Organic Synthesis*; Wiley: New York, 1990; Collect. Vol. VII, p 232