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Synthesis of Tetrasubstituted and Functionalized Enol Ethers by *E*-Selective Olefination of Esters with Ynolates

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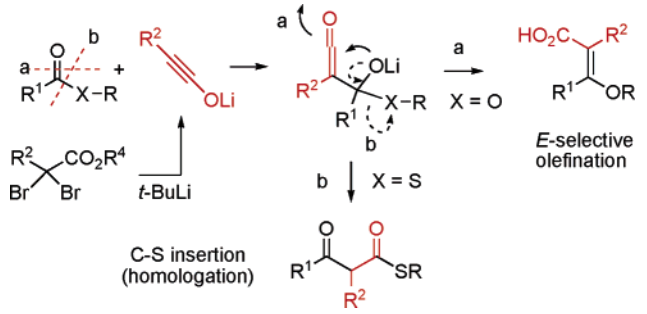
Esters are versatile electrophiles for carbon−carbon bond formation, which includes Claisen condensation and related acylations.[1] Although olefination of ester carbonyls would appear to be useful for the synthesis of enol ethers, conventional methods such as the Wittig reaction generally have been unsuccessful in realizing olefination[2] due to the lower electrophilicity of esters. Instead, metal carbenoids, such as Tebbe reagents, are used to accomplish this transformation; however, they are limited to the preparation of simple enol ethers.[3] The stereocontrolled synthesis of multisubstituted and functionalized enol ethers via olefination therefore still remains a challenge for organic chemists. If a new, reactive olefination reagent were available, this problem essentially could be overcome. Over the past few years, we have developed the torquoselective olefination of aldehydes, ketones, and acylsilanes with ynolates[4] via ring-opening of β-lactone enolates and have demonstrated the versatility of ynolates as olefination reagents.[5] Herein, we describe the first highly stereoselective synthesis of tetrasubstituted, functionalized (*E*)-enol ethers via olefination of esters with ynolates and also report the homologation of thiol esters with C−S insertion (Scheme 1).

Scheme 1



We first examined the reaction of *O*-alkyl esters with ynolates (Scheme 2). At −78 °C, the ynolate, generated by treatment of phenyl 2,2-dibromopropanoate[6] with *tert*-butyllithium,[7] did not react with ethyl benzoate; however, at room temperature, the starting ester disappeared in 1 h. Consequently, the enol ether, β-ethoxy-α,β-unsaturated carboxylic acid, was obtained in 94% yield with an *E*/*Z* ratio of 89/11 (Table 1, entry 1). Encouraged by this result, we decided to survey the generality for the olefination of esters, as shown in Table 1. While the olefination of ethyl *p*-methoxybenzoate (**1b**) gave the desired olefin **3ba** in good yield with moderate selectivity (entry 2), ethyl *p*-nitrobenzoate (**1c**) afforded the product **3ca** with higher *E*-selectivity (entry 3). Aliphatic and unsaturated esters provided olefins with excellent *E*-selectivities in good yields (entries 4−13). Sterically hindered and aromatic ynolates can also be used in this olefination (entries 6 and 7). The fact that allyl and *tert*-butyl esters, as well as ethyl esters, could furnish olefins with excellent *E*-selectivities would indicate that this olefination can be used for the preparation of enol ethers bearing intricate *O*-alkyl groups. Acetal and siloxy functions were tolerated during the reaction (entries 10 and 11). It should be noted that excellent yields and selectivities were achieved using α-amino esters derived from L-amino acids (entries 12 and 13).[8] Compared with the corresponding allyl ester **1f** without an amino group, this tendency toward higher efficiency was outstanding. From these results, we have demonstrated the versatility and generality of this olefination of esters via their reaction with ynolates.

Scheme 2

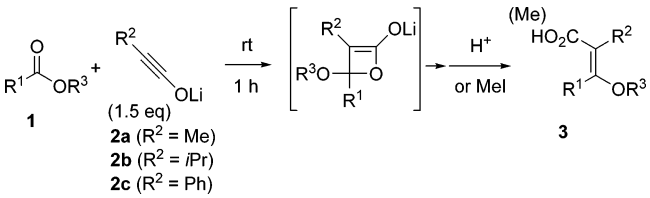
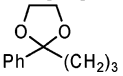
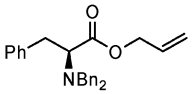
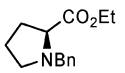


Table 1. Olefination of Esters via Reaction with Ynolates

entry	esters: 1	R¹	R³	R²	3	yield /%	*E*:*Z*
1	**1a**	Ph	Et	Me	**3aa**	94	89:11
2	**1b**	*p*-MeOC$_6$H$_4$	Et	Me	**3ba**	90	77:23
3	**1c**	*p*-NO$_2$C$_6$H$_4$	Et	Me	**3ca**	95	98:2
4	**1d**	PhCH$_2$CH$_2$	Et	Me	**3da**	79	>99:1
5	**1e**	(*E*)-PhCH=CH	Et	Me	**3ea**	78	>99:1
6	**1d**	PhCH$_2$CH$_2$	Et	*i*-Pr	**3db**	65[b]	>99:1
7	**1d**	PhCH$_2$CH$_2$	Et	Ph	**3dc**	61[b]	>99:1
8	**1f**	PhCH$_2$CH$_2$	allyl	Me	**3fa**	47[a]	>99:1
9	**1g**	PhCH$_2$CH$_2$	*t*-Bu	Me	**3ga**	44[b]	>99:1
10	**1h**		Et	Me	**3ha**	82[b]	>99:1
11	**1i**	TBDPSO(CH$_2$)$_5$	Et	Me	**3ia**	81[b]	>99:1
12	**1j**			Me	**3ja**	92	>99:1
13	**1k**			Me	**3ka**	>99	>99:1

[a] A small amount of β-keto ester was obtained as a side product. [b] Isolated as the methyl ester.

To trap the intermediate β-lactone, the reaction mixture was quenched at −30 °C; however, only the carboxylic acid was obtained, suggesting that the β-lactone enolate, the most probable intermediate, immediately ring-opens as the cycloaddition proceeds. The *E*/*Z* selectivity would be controlled in the electrocyclic ring-opening of the β-lactone enolate, as described in our previous

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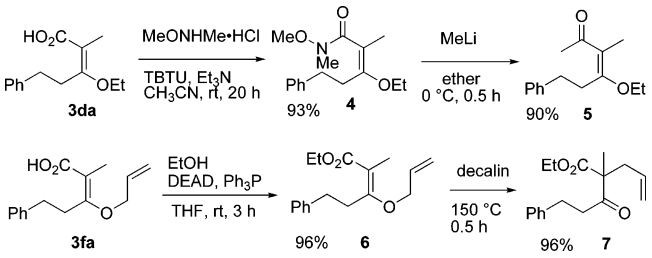
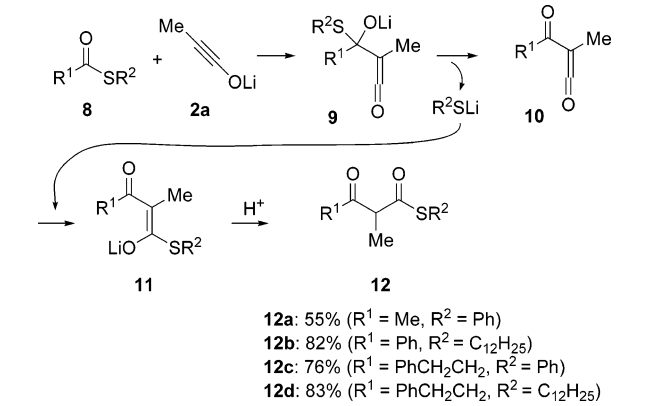
Scheme 3



Scheme 4



12a: 55% (R^1 = Me, R^2 = Ph)
12b: 82% (R^1 = Ph, R^2 = $C_{12}H_{25}$)
12c: 76% (R^1 = $PhCH_2CH_2$, R^2 = Ph)
12d: 83% (R^1 = $PhCH_2CH_2$, R^2 = $C_{12}H_{25}$)

reports.[5] The preferential generation of the *E*-form indicates outward rotation of the alkoxy substituent on the oxetene (β-lactone enolate). These results can be elucidated by Houk's torquoselectivity, which shows that electron-donating substituents, such as alkoxy groups, rotate outward.[5e,9]

The olefinated products, α,β-substituted (*E*)-β-alkoxyacrylic acids, were converted to synthetically useful intermediates. For example, the carboxylic acid **3da** was transformed to the Weinreb amide **4**,[10] which was reacted with methyllithium to give the methyl ketone **5** in good yield (Scheme 3). The Claisen rearrangement of the β-allyloxyacrylic ester **6**, prepared from **3fa**, furnished the β-keto ester **7** bearing a quaternary carbon in good yield. These transformations demonstrate the high potential of β-alkoxy acrylic acids in synthetic organic chemistry.

In contrast to esters, thiol esters **8** did not provide the olefins, but instead gave the homologated β-keto thiol esters **12** in good yields (Scheme 4). The efficient elimination of the thiolates (R^2-SLi) from the initial adducts **9**, formed by the addition of the ynolates to **8**, would be followed by the attack of the thiolate on the resulting α-keto ketene **10** to afford the β-keto thiol ester enolates **11**. Both esters of dodecanethiol and thiophenol provided the desired β-keto thiol esters **12** in good yields. This homologation can be formally regarded as the insertion of the ynolate carbon framework into the C−S bond of thiol esters, which is a new type of Claisen condensation. This olefination-insertion switching would depend on the leaving-group ability of the (thio)alkoxides.[11]

In conclusion, we have developed the first stereoselective olefination of esters affording tetrasubstituted, functionalized enol ethers, which are useful synthetic intermediates for various C−C bond formations. We also have found a new homologation of thiol esters giving β-keto thiol esters. The reaction mode changes depending especially on the leaving-group ability of the corresponding alkoxide or thioalkoxide on the ester. This methodology with ynolates could be applied to a wide variety of esters and related carbonyl compounds. Synthetic applications are now in progress in our laboratory.

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Supporting Information Available: Characterization of new compounds, general procedures (PDF), and X-ray crystal structures (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a review, see: Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 795−863.
(2) Nonclassical Wittig reagents undergo olefination of esters. See: Tsunoda, T.; Takagi, H.; Takada, D.; Kaku, H.; Ito, S. *Tetrahedron Lett.* **2000**, *41*, 235−237.
(3) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212−1216. (c) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270−3272. (d) Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907−915. (e) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394. (f) Petasis, N. A.; Bzowej, E. I. *J. Org. Chem.* **1992**, *57*, 1327−1330. (g) Petasis, N.; Akritopoulou, I. *Synlett* **1992**, 665−667. (h) Petasis, N. A.; Bzowej, E. I. *Tetrahedron Lett.* **1993**, *34*, 943−946. (i) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4412−4414. (j) Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1065−1068. (k) Matsubara, S.; Ukai, K.; Mizuno, T.; Utimoto, K. *Chem. Lett.* **1999**, 825−826. (l) Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127−1128. (m) Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* **1998**, *63*, 7286−7288. (n) Takeda, T.; Watanabe, M.; Rahim, M. A.; Fujiwara, T. *Tetrahedron Lett.* **1998**, *39*, 3753−3756. (o) Rahim, M. A.; Sasaki, H.; Saito, J.; Fujiwara, T.; Takeda, T. *Chem. Commun.* **2001**, 625−626. (p) Takeda, T.; Shimane, K.; Ito, K.; Saeki, N.; Tsubouchi, A. *Chem. Commun.* **2002**, 1974−1975. (q) Yan, T.-H.; Chien, C.-T.; Tsai, C.-C.; Lin, K.-W.; Wu, Y.-H. *Org. Lett.* **2004**, *6*, 4965−4967.
(4) For reviews, see: (a) Shindo, M. *Synthesis* **2003**, 2275−2288. (b) Shindo, M. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 1155−1166. (c) Shindo, M. *Yakugaku Zasshi* **2000**, *120*, 1233−1246. (d) Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367−374.
(5) (a) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857−4860. (b) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2000**, *65*, 5443−5445. (c) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840−6841. (d) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912−3916. (e) Mori, S.; Shindo, M. *Org. Lett.* **2004**, *6*, 3945−3948. (f) Shindo, M.; Yoshikawa, T.; Itou, Y.; Mori, S.; Nishii, T.; Shishido, K. *Chem.−Eur. J.* **2006**, *12*, 524−536.
(6) Shindo, M.; Sato, Y.; Koretsune, R.; Yoshikawa, T.; Matsumoto, K.; Itoh, K.; Shishido, K. *Chem. Pharm. Bull.* **2003**, *51*, 477−478.
(7) (a) Shindo, M. *Tetrahedron Lett.* **1997**, *38*, 4433−4436. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411−2422. (c) Shindo, M.; Koretsune, R.; Yokota, W.; Itoh, K.; Shishido, K. *Tetrahedron Lett.* **2001**, *42*, 8357−8360.
(8) The product was obtained without loss of optical purity.
(9) (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989−7991. (b) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099−2111. (c) Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471−477.
(10) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927−1930.
(11) The reaction of phenyl benzoate with ynolate **2a** gave no olefin but gave the β-keto phenyl ester in ca. 30% yield. The allyl ester (Table 1, entry 8, footnote a) also produced the homologated product as a side product.

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