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Virtually Complete *E*-Selective α,*β*-Unsaturated Ester Synthesis by $Hg(OTf)_2$-Catalyzed Hydration of *sec*-Ethoxyalkynyl Acetate

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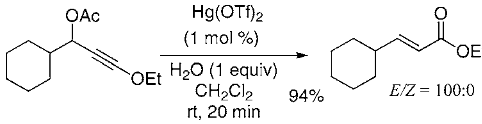
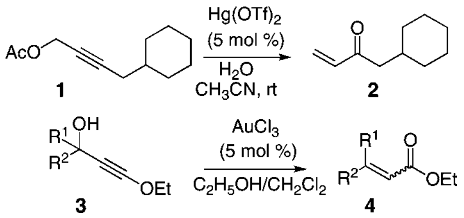
ABSTRACT



The reaction of alkyl-substituted *sec*-ethoxyalkynyl acetates with water catalyzed by $Hg(OTf)_2$ afforded α,*β*-unsaturated esters in excellent yield with high catalytic turnover up to 1000 times under very mild reaction conditions with virtually complete *E*-selectivity, superior even to that of the HWE reaction.

α,*β*-Unsaturated esters, which have functional importance as versatile building blocks in organic synthesis and as constituents of biologically active compounds, are mostly prepared by Wittig reaction or Horner−Wadsworth−Emmons (hereafter HWE) reaction in a generally *E*-selective manner.[1] Although a number of alternative procedures to overcome the drawbacks of the Wittig reaction have been reported, *E*-selectivity is not always very high, and even the HWE reaction affords small amounts of *Z*-isomer. Thus, troublesome separation of two isomers is required.[2] Acid-catalyzed rearrangement of propargyl alcohol to an α,*β*-unsaturated carbonyl compound is an important synthetic procedure known as the Meyer−Shuster and Rupe rearrangement.[3] However, these reactions have been applicable only for *tert*- and *sec*-alcohols. We have recently found that the mercuric triflate [hereafter $Hg(OTf)_2$] showed highly efficient catalytic activity for the hydration of propargyl acetate **1** leading to enone **2** that corresponds to a Meyer−Schuster-type reaction applicable to a primary alcohol (Scheme 1).[4] This effective catalytic activity is based upon a significant π-philicity of $Hg(OTf)_2$ as well as an efficient protodemercuration sequence to regenerate the catalyst.[5] Engel and Dudley recently reported a gold(III)-catalyzed Meyer−Schuster rearrangement of ethoxyalkynyl alcohol **3** to give α,*β*-unsaturated ester **4**.[6] However, this procedure generates a mixture of *E*- and *Z*-isomers. In this communication, we describe $Hg(OTf)_2$-catalyzed hydration of alkyl-

Scheme 1



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(1) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927. (b) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369−379. (c) Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. *Tetrahedron Lett.* **2005**, *46*, 4473−4477.

(2) (a) List, B.; Doehring, A.; Fonseca, M. T. H.; Job, A.; Torres, R. R. *Tetrahedron* **2006**, *62*, 476−482. (b) Sun, W.; Yu, B.; Kuhn, F. E. *Tetrahedron Lett.* **2006**, *47*, 1993−1996. (c) Zeitler, K. *Org. Lett.* **2006**, *8*, 637−640. (d) Concellon, J. M.; Concellon, C.; Mejica, C. *J. Org. Chem.* **2005**, *70*, 6111−6113. Further references are cited therein.

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substituted *sec*-ethoxyalkynyl acetate to give α,*β*-unsaturated esters in excellent yield under very mild conditions with high catalytic turnover and virtually complete *E*-selectivity that is superior not only to the Wittig reaction but also to the HWE reaction from the standpoint of atom economy and stereoselectivity.[1,2]

Scheme 2

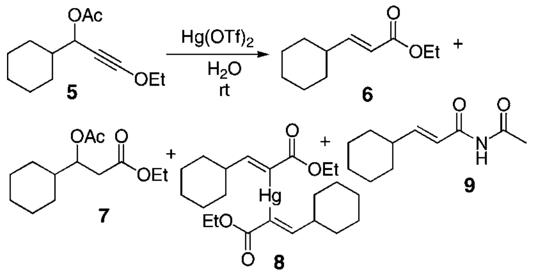

Table 1. Hg(OTf)$_2$-Catalyzed Hydration of **5**

entry	solvent	Hg(OTf)$_2$ (mol %)	H$_2$O (equiv)	time (min)	yield (%)[a] **6**	**7**	**8**	**9**
1	CH_3CN	5	1.5	30	62	2	5	21
2	$C_6H_5CH_3$	5	1.5	1440	51	19	1	–
3	Et_2O	5	1.5	150	34	44	5	–
4	CH_3NO_2	5	1.5	40	72	7	3	–
5	CH_2Cl_2	5	1,5	30	76	3	–	–
6	CH_2Cl_2	10	1.5	10	75	5	–	–
7	CH_2Cl_2	1	1.5	20	88	4	–	–
8	CH_2Cl_2	1	1	20	94	6	–	–
9	CH_2Cl_2	1	5	15	76	8	1	–
10	CH_2Cl_2	1	1[b]	20	86	8	–	–
11	CH_2Cl_2	1	–	20	25[c]	–	–	–
12	CH_2Cl_2	1[d]	1	20	84	3	–	–
13	CH_2Cl_2	0.1	1	300	85	11	–	–
14	CH_2Cl_2	0.1[d]	1	300	20[c]	–	–	–

[a] NMR yield using 1,1,1-trichloroethane as an internal standard. [b] Reaction in the presence of *n*-Bu_4NOTf (1 equiv). [c] More than 70% of **5** was recovered. [d] Reaction by using TfOH as catalyst.

We first examined the reaction of **5** with 1.5 equiv of H_2O in the presence of 5 mol % of Hg(OTf)$_2$ in acetonitrile at room temperature (Scheme 2). The reaction was completed within 30 min, and an α,*β*-unsaturated ester **6** was obtained in 63% yield (NMR yield 62% by using 1,1,1-trichloroethane as an internal standard)[6b] after column chromatography on silica gel along with acetoxy ester **7** (2%), dimeric vinylmercuric product **8** (5%), and Ritter-type byproduct **9** (21%)[7] (Table 1, entry 1). The geometry of the double bond of **6** was probed to be *E*, and no trace of *Z*-isomer was detected. While the generation of **9** was prevented by carrying out the reaction in toluene, the reaction was very slow, giving rise to **6** in 51% yield after 24 h (entry 2). The best solvent was shown to be dichloromethane, which afforded **6** in 76% yield along with 3% of **7** and negligible amounts of vinylmercury product **8** (entry 5). Although an increase of catalyst loading to 10 mol % did not increase the yield of **6**, 1 mol % of catalyst resulted in an 88% yield within 20 min (entries 6 and 7). The best result was obtained with the reaction using 1 mol % of Hg(OTf)$_2$ and 1 equiv of H_2O for 20 min at room temperature in dichloromethane, affording **6** in 94% yield along with 6% of acetoxy ester **7** (entry 8). The reaction was sensitive to the quantity of H_2O: more than 5 equiv of H_2O significantly decreased the yield of **6** (entry 9). Addition of a phase transfer catalyst such as *n*-Bu_4NOTf did not improve either reaction rate or yield of **6** (entry 10). Reaction under anhydrous condition also provided **6** in 25% yield along with 71% of starting material after 20 min (entry 11). The reaction was shown to be also possible by using TfOH, which gave rise to **6** in 84% yield with complete *E*-selectivity along with 3% of **7** (entry 12);[8] however, the efficiency of Hg(OTf)$_2$ over TfOH was evident when the reaction was carried out by using 0.1 mol % of catalyst. Hg(OTf)$_2$ afforded **6** in 85% yield after 5 h (entry 13) along with 11% of **7**, whereas 0.1 mol % of TfOH gave **6** in 20% yield along with 76% of starting material after 5 h (entry 14).[9]

The proposed mechanism of this Hg(OTf)$_2$-catalyzed hydration is as shown in Scheme 3. The reaction is initiated

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(3) (a) Meyer, K. H.; Schuster, K. *Chem. Ber.* **1922**, *55*, 819−821. (b) Rupe, H.; Kambli, E. *Helv. Chim. Acta* **1926**, *9*, 672. (c) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429−438. (d) Chabardes, P. *Tetrahedron Lett.* **1988**, *29*, 6253−6256. (e) Narasaka, K.; Kusama, H.; Hayashi, Y. *Chem. Lett.* **1991**, 1413−1416. (f) Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059−2068. (g) Mercier, C.; Chabardes, P. *Pure Appl. Chem.* **1994**, *66*, 1509−1518. (h) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Tetrahedron Lett.* **2002**, *43*, 7531−7533. (i) Cadierno, V.; Diez, J.; Garcia-Garrido, S. E.; Gimeno, J. *Chem. Commun.* **2004**, 2716−2717. (j) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147−2150.

(4) Imagawa, H.; Asai, Y.; Takano, H.; Hamagaki, H.; Nishizawa, M. *Org. Lett.* **2006**, *8*, 447−450.

(5) (a) Nishizawa, M.; Skwarczynski, M.; Imagawa, H.; Sugihara, T. *Chem. Lett.* **2002**, 12−13. (b) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609−1611. (c) Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563−4565. (d) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679−3681. (e) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451−453. (f) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Synlett* **2005**, 703−705. (g) Imagawa, H.; Kinoshita, A.; Fukuyama, T.; Yamamoto, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 4729−4731. (h) Yamamoto, H.; Nishiyama, M.; Imagawa, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 8369−8373. (i) Kurisaki, T.; Naniwa, T.; Yamamoto, H.; Imagawa, H.; Nishizawa, M. *Tetrahedron Lett.* **2007**, *48*, 1871−1874. (j) Yamamoto, H.; Sasaki, I.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2007**, *9*, 1399−1402. (k) Yamamoto, H.; Pandey, G.; Asai, Y.; Nakano, M.; Kinoshita, A.; Namba, K.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2007**, *9*, 4029−4032.

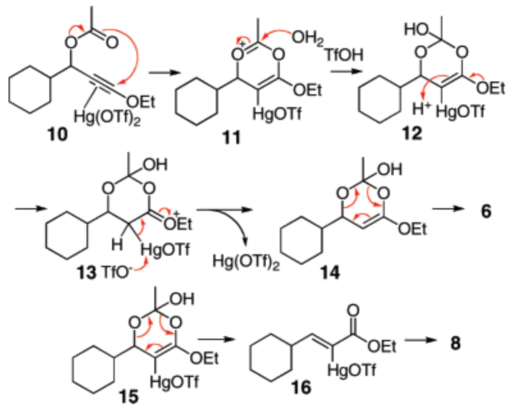
(6) (a) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027−4029. (b) Lopez, S. S.; Engel, D. A.; Dudley, G. B. *Synlett* **2007**, 949−953.

(7) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4045−4048.

(8) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C. G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175−4178.

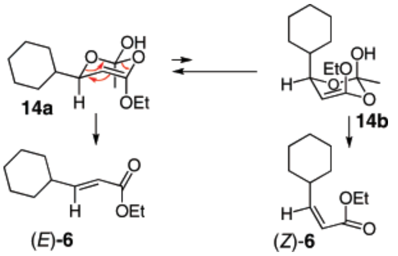
(9) Typical procedure: To a solution of **5** (100 mg, 0.45 mmol) in dichloromethane (4.5 mL) were sequentially added H_2O (8.0 μL, 0.45 mmol) and Hg(OTf)$_2$ (0.1 M solution in acetonitrile, 45 μL, 0.0045 mmol) at room temperature, and the mixture was stirred for 20 min at the same temperature. After addition of $NaHCO_3$ solution, organic material was extracted with dichloromethane. Dried and concentrated extract was purified by flash column chromatography on silica gel using hexane−ethyl acetate (15:1) as an eluent to give **6** (74.7 mg, 92%, NMR yield 94%) as a colorless oil: FTIR (neat) 2928, 2853, 1725, 1650, 1448, 1368, 1274, 1173, 1046, 983 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.92 (dd, J = 15.4, 6.6 Hz, 1H), 5.76 (dd, J = 15.4, 1.6 Hz, 1H), 4.18 (q, J = 7.2 Hz, 1H), 2.13 (m, 1H), 1.60−1.85 (m, 6H), 1.29 (t, J = 7.2 Hz, 1H), 1.01−1.45 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.1, 154.2, 118.9, 60.1, 40.4, 31.7, 25.9, 25.7, 14.2; HRMS *m/z* calcd for $C_{11}H_{19}O_2^+$ $[M + H]^+$ 183.1386, found 183.1384.

Scheme 3. Proposed Mechanism of $Hg(OTf)_2$-Catalyzed Hydration of Ethoxyalkynyl Acetate



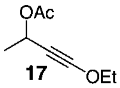
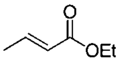
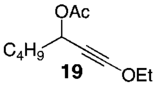
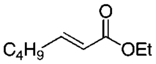
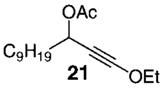
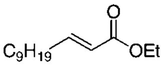
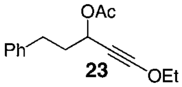
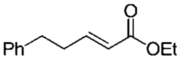
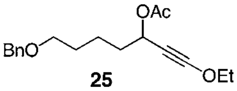
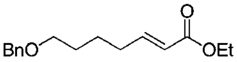
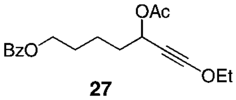
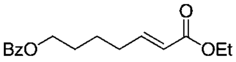
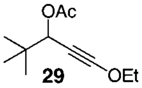
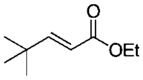
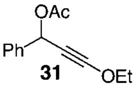
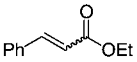
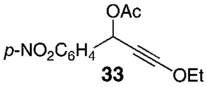
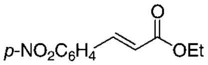
by π-complexation of alkyne with $Hg(OTf)_2$, as shown in **10**, and generates oxonium cation **11** via participation of the acetyl group. Nucleophilic addition of water to **11** affords vinylmercury intermediate **12**. Protonation by TfOH formed in situ generates alternative oxonium cation **13**, which undergoes demercuration to produce the orthoester-type intermediate **14** and the regenerated catalyst $Hg(OTf)_2$. A 6-π electrocyclic fragmentation should yield α,β-unsaturated ester **6**. When the illustrated fragmentation of **15** takes place prior to the protonation, the byproduct **8** should form via **16** that does not favor for the protodemercuration sequence (Scheme 4).

Scheme 4. Possible Transition States Leading to (*E*)-**6** and (*Z*)-**6**



The virtually complete *E*-selectivity could be explained by considering the transition state that is in an equilibrium between an equatorial **14a** and an axial **14b** conformation. The stability of **14a** over **14b** is obvious and leads to preferential formation of (*E*)-**6**.

Table 2. $Hg(OTf)_2$-Catalyzed Hydration of Ethoxypropargyl Acetates in Dichloromethane

substrate	time (min)	product (yield) [a]
 **17**	40	 **18** (95%) *E/Z* 100:0
 **19**	30	 **20** (60%) *E/Z* 100:0
 **21**	40	 **22** (95%) *E/Z* 100:0
 **23**	120	 **24** (89%) *E/Z* 100:0
 **25**	30	 **26** (99%) *E/Z* 100:0
 **27**	30	 **28** (79%) *E/Z* 100:0
 **29**	120	 **30** (45%) *E/Z* 100:0
 **31**	40	 **32** (77%) *E/Z* 50:50
 **33**	1440	 **34** (100%) *E/Z* 5:1

[a] NMR yield using 1,1,1-trichloroethane as an internal standard.

The hydration of various ethoxyalkynyl acetates was next examined. The reaction of 4-ethoxy-3-butyn-2-ol derivative **17** with H_2O (1 equiv) in the presence of 1 mol % of $Hg(OTf)_2$ in dichloromethane at room temperature for 30 min afforded the well-known (*E*)-ethyl crotonate (**18**) in 95% yield (NMR using 1,1,1-trichloroethane as the internal standard) (Table 2). The *Z*-isomer was not detected at all. When acetaldehyde was reacted with diethyl phosphonoacetate under the standard HWE conditions, this afforded **18**; however, this was a 12.5:1 mixture of *E*- and *Z*-isomers (see NMR charts in Supporting Information). This result indicates that our procedure is characterized by the generation of conjugate esters with complete *E*-selectivity. Although the reaction of long alkyl chain analogue **21** also provided conjugate ester **22** in 95% yield,[6b] reaction of heptyn-3-ol derivative **19** resulted in only 60% yield of **20**,[6b] together with an unidentified byproduct.[10] Substituted alkyl analogues **23**, **25**, and **27** afforded esters **24**,[2b] **26**,[11a] and **28**,[11b] respectively, in satisfactory yields. Reaction of *tert*-butyl-substituted **29** resulted in modest yield of **30**.[6b] While phenyl-substituted **31** also afforded ester **32** in 77% yield;[6b] however, the product was an 1:1 mixture of *E*- and *Z*-isomers. *p*-Nitrophenyl-substituted **33** gave **34**[2b] in quantitative yield with *E/Z* 5:1 selectivity, though this required a long reaction time.

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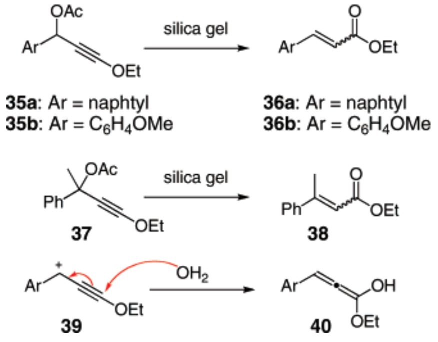
[10] This reaction was repeated five times, and **20** was obtained in 55−60% yield.

[11] (a) Chang, M. Y.; Chen, C. Y.; Chen, S. T.; Chang, N. C. *Tetrahedron* **2003**, *59*, 7547−7553. (b) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377−1393. (c) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473−9474.

Ethoxyalkynyl acetates **17**, **19**, **21**, **23**, **25**, **27**, **29**, **31**, and **33** were prepared from the corresponding aldehydes by the alkylation with Li acetylide of ethoxyacetylene and subsequent acetylation in excellent yields. Although naphthyl- and *p*-methoxyphenyl-substituted acetates **35a** and **35b** were prepared by the same procedure, these products were unstable on silica gel column chromatography and decomposed to give 1:1 mixtures of *E* and *Z* conjugate esters **36a** and **36b**,[2d] respectively (Scheme 5). *tert*-Acetate **37** was more unstable and decomposed to yield a 1:1 mixture of conjugate esters **38** during column chromatography on silica gel.[11c] These results as well as the mixture formation of **32** from **31** suggest that the reactions of these aromatic derivatives probably take place via the Meyer−Shuster reaction by forming stable propargylic cation **39** followed by hydration forming **40**. Thus this procedure is not applicable for substrates containing cation stabilizing functionality.

Scheme 5. Silica Gel Induced Hydration via Stable Cation



Thus, we have established an efficient procedure for synthesis of alkyl-substituted α,*β*-unsaturated esters by the hydration of *sec*-ethoxyalkynyl acetate catalyzed by $Hg(OTf)_2$ under the very mild reaction conditions with very high catalytic turnover. The procedure is particularly noteworthy in its virtually complete *E*-selectivity that is even higher than that obtained with the HWE reaction.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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