DOI 10.5012/bkcs.2010.31.03.742

Synthesis of (*E*)-α-Ethynyl-α,β-unsaturated Esters from Allenyl Acetates Catalyzed by DABCO and Their Application to Sonogashira Cross-Coupling Reactions†

Hyunseok Kim, Doosup Shin, Kwangmoo Lee, Sangkyu Lee, Sanghyuk Kim, and Phil Ho Lee*

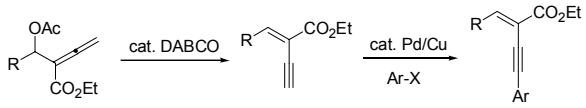
*Department of Chemistry and Institute for Molecular Science and Fusion Technology, Kangwon National University, Chuncheon 200-701, Korea. *E-mail: phlee@kangwon.ac.kr*
Received January 23, 2010, Accepted February 1, 2010

Key Words: Allenyl acetate, Catalysis, Enyne, (*E*)-α-Ethynyl-α,β-unsaturated ester, DABCO

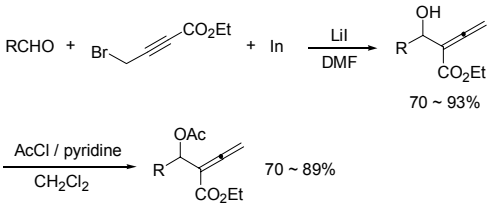
Because synthesis of α-ethynyl-α,β-unsaturated esters is one of the challenging problems in synthetic organic chemistry,[1] many efficient synthetic methods for the preparation of these compounds have been reported.[2] However, the need for a highly selective synthetic method of (*E*)-α-ethynyl-α,β-unsaturated esters has been remained.[1] Generally, the selective synthesis of these compounds was accomplished by the transition metal-catalyzed cross-coupling reactions of (*Z*)-α-halo-α,β-unsaturated esters with terminal alkynes through Sonogashira cross-coupling reaction. Nevertheless, this method is limited because the selective synthetic method of (*Z*)-α-halo-α,β-unsaturated esters is difficult and isomerization is somewhat occurred during the cross-coupling reactions. Although selective synthesis of (*Z*)-α-halo-α,β-unsaturated esters *via* $CrCl_2$-mediated olefinations of aldehydes with trihaloacetates was reported,[3] the preparation of (*Z*)-α-halo-α,β-unsaturated esters through bromination-dehydrobromination,[4] rearrangements,[5] alkoxycarbonylation,[6] deoxygenation of glycidic esters,[7] thermal eliminations,[8] or Wittig/Horner-Emmons/Peterson-type condensations[9] often suffer from poor stereoselectivities, unsatisfactory yields, costly reagents, and/or lengthy procedures.[10] Therefore, we tried to prepare selectively (*E*)-α-ethynyl-α,β-unsaturated esters from another precursor without the use of (*Z*)-α-halo-α,β-unsaturated esters. As part of our continuing studies into the utility of allene groups,[11] we report herein the preparation of the selective synthesis of (*E*)-α-ethynyl-α,β-unsaturated esters from allenyl acetates catalyzed by DABCO and their application to Sonogashira cross-coupling reaction (Scheme 1).

First, various allenyl acetates were prepared from the reaction of aldehydes with organoindium in situ generated from ethyl 4-bromobutynoate and indium in the presence of lithium iodide in DMF followed by acetylation (Scheme 2).[11k]

Next, allenyl acetates were treated with various acids or bases (Table 1). Allenyl acetate (**1d**) did not react with PPTS and AcOH (entries 1 and 2). Surprisingly, treatment of **1d** with pyridine (0.2 equiv) in DMF selectively produced ethyl (*E*)-α-ethynyl cinnamate (**2d**) in 75% yield (entry 3). *E* selectivity was determined by the chemical shift of the vinyl proton in **2d**. Vinyl proton in *E* isomer of **2d** appeared at upfield due to the shielding effect from the ester group.[10h] Encouraged by this result, triphenylphosphine and DABCO were subsequently examined. Use of triphenylphosphine (0.2 equiv) provided **2d** in 69% yield in DMF for 0.5 h (entry 4). In the case of DABCO (0.2 equiv), the desired product **2d** was selectively produced in 75% yield in DMF (entry 5). DMF was the best solvent among several reaction media examined (DMF, THF and CH_3CN) (entries 5-7). Of the reactions screened, the best results were obtained with DABCO (0.1 equiv) in DMF at 25 °C for 2.5 h, producing selectively **2d** in 81% yield (entry 8). There is no ethyl (*Z*)-α-ethynyl cinnamate formed in any reactions.



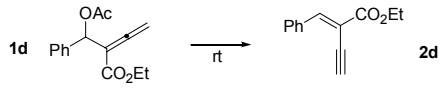
Scheme 1. Selective preparation of (*E*)-α-ethynyl-α,β-unsaturated esters



R= *n*-Bu, C_6H_{11}, PhCH=CBr, Ph, 4-Cl-C_6H_4, 3-Br-C_6H_4
2,4,6-Me_3-C_6H_2, 3-MeO-C_6H_4, 3,5-$(MeO)_2$-C_6H_3
3,4-(OCH_2O)-C_6H_3, 4-Ac-C_6H_4, 4-MeO_2C-C_6H_4, 2-Furyl

Scheme 2. Preparation of allenyl acetates

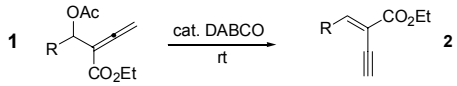
Table 1. Reaction optimization



entry	reagent (equiv)	solvent	time (h)	yield (%)
1	PPTS (0.2)	CH_2Cl_2	6	0
2	AcOH (0.2)	DMF	12	0
3	Pyridine (0.2)	DMF	0.67	75
4	PPh_3 (0.2)	DMF	0.5	69
5	DABCO (0.2)	DMF	0.5	75
6	DABCO (0.2)	THF	4.5	50
7	DABCO (0.2)	CH_3CN	4.5	70
8	DABCO (0.1)	DMF	2.5	81

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.

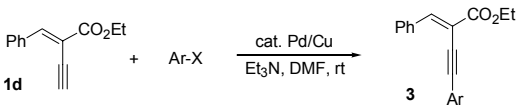
Table 2. Synthesis of (*E*)-α-ethynyl-α,β-unsaturated esters[a]



entry	R		time (h)	product (**2**)	yield (%)
1	*n*-Bu	**1a**	3.5	**2a**	72
2	C_6H_{11}	**1b**	4	**2b**	82
3	PhCH=CBr	**1c**	1	**2c**	70
4	Ph	**1d**	2.5	**2d**	81
5	4-Cl-C_6H_4	**1e**	0.5	**2e**	86
6	3-Br-C_6H_4	**1f**	0.5	**2f**	88
7	2-I-C_6H_4	**1g**	1	**2g**	73
8	2,4,6-Me_3-C_6H_2	**1h**	3	**2h**	84
9	3-MeO-C_6H_4	**1i**	2	**2i**	72
10	3,5-$(MeO)_2$-C_6H_3	**1j**	1	**2j**	80
11	3,4-(OCH_2O)-C_6H_3	**1k**	1	**2k**	80
12	4-Ac-C_6H_4	**1l**	0.5	**2l**	81
13	4-MeO_2C-C_6H_4	**1m**	0.5	**2m**	81
14	2-Furyl	**1n**	0.5	**2n**	84

[a]10 mol % DABCO was used.

Table 3. Synthesis of (*E*)-α-alkynyl-α,β-unsaturated esters[a]

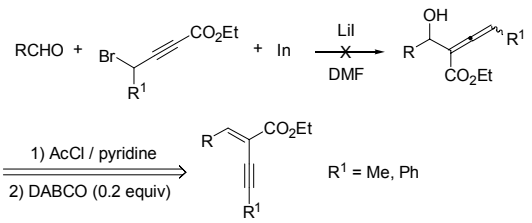


entry	Ar	X	time (h)	product	yield (%)
1	Ph	I	0.5	**3a**	40[b]
2	Ph	I	0.5	**3a**	50[b,c]
3	Ph	I	0.5	**3a**	25[b,d]
4	Ph	I	0.5	**3a**	80
5	4-EtO_2C-C_6H_4	I	0.4	**3b**	90
6	4-*n*-Bu-C_6H_4	I	0.4	**3c**	83
7	3-MeO-C_6H_4	I	0.7	**3d**	64
8	2-Ac-C_6H_4	I	2	**3e**	77
9		OTf	0.4	**3f**	74

[a]2 mol % $Pd_2dba_3CHCl_3$/16 mol % Ph_3P, 10 mol % CuI, 1.5 equiv of R-X and equiv of Et_3N were used. [b]5 mol % $PdCl_2(PPh_3)_2$ instead of $Pd_2dba_3CHCl_3$ and PPh_3 was used. [c]THF was used. [d]CH_3CN was used.

We applied the catalytic system to a variety of allenyl acetates (Table 2). Allenyl acetate **1a** derived from the reaction of 1-butanal with organoindium in situ generated from ethyl 4-bromobutynoate and indium followed by acetylation was treated with DABCO (0.1 equiv) in DMF for 3.5 h to produce selectively ethyl 2(*E*)-ethynyl-2-hexenoate (**2a**) in 72% yield (entry 1). In the case of allenyl acetate obtained from cyclohexanecarbaldehyde, ethyl 2(*E*)-ethynyl-3-cyclohexylacrylate **2b** was selectively obtained in 82% yield (entry 2). Allenyl acetate **1c** gave rise to the corresponding (*E*)-α-ethynyl-α,β-unsaturated ester **2c** in 70% yield (entry 3). Altering the electron demand of the substituents on aromatic rings did not diminish the efficiency and selectivity (entries 5-13). Allenyl acetates (**1e**, **1f** and **1g**) possessing 4-chlorophenyl,3-bromophenyl and 2-iodophenyl group were cleanly converted to the desired products (**2e**, **2f** and **2g**) in excellent yields (entries 5-7). Treatment of allenyl acetates having 2,4,6-trimethylphenyl and 3,5-dimethoxyphenyl group with DABCO (0.1 equiv) provided selectively (*E*)-α-ethynyl-α,β-unsaturated esters (**2h** and **2j**) in 84% and 80% yields, respectively (entries 8 and 10). The present method worked equally well with allenyl acetates (**1l** and **1m**) bearing electron-withdrawing groups such as ketone and ester group were employed (entries 12 and 13). Allenyl acetate (**1n**) possessing furyl group turned out to be compatible with the reaction conditions (entry 14). Surprisingly, no (*Z*)-α-ethynyl-α,β-unsaturated esters are formed in any reactions. Unfortunately, tetrasubstituted alkenes bearing ethynyl group were not prepared because organoindium in situ generated from ethyl 4-bromobutynoate and indium did not react with ketone compound.

We attempted the reaction of ethyl 4-bromobutynoate having methyl or phenyl group at 4-position with indium in the presence of several additives to prepare (*E*)-α-alkynyl-α,β-unsaturated esters but we could not obtain the corresponding allenyl alcohol.



Alternatively, (*E*)-α-alkynyl-α,β-unsaturated esters could be selectively obtained in good to excellent yields without isomerization through Sonogashira cross-coupling reaction (Table 3). Enyne **1d** reacted with iodobenzene using 5 mol % $PdCl_2(PPh_3)_2$, 10 mol % CuI and Et_3N (2 equiv) in DMF, THF and acetonitrile, producing the cross-coupling product **3a** in 40%, 50% and 25% yields, respectively (entries 1-3). However, reaction of **1d** with iodobenzene in the presence of 2 mol % $Pd_2dba_3CHCl_3$, 16 mol % PPh_3, 10 mol % CuI and Et_3N (2 equiv) in DMF gave the desired product *E*-**3a** in 80% yield (entry 4). For a large number of aryl iodides, the presence of various substituents such as ethoxycarbonyl, *n*-butyl, methoxy and acetyl group on the aromatic ring showed little affect efficiency of the reactions (entries 5-8). We were pleased to obtain the cross-coupling product **3f** in 74% yield from treatment of **1d** with vinyl triflate under the

optimum reaction conditions (entry 9).

In summary, we have developed the selective synthetic method of (*E*)-α-ethynyl-α,β-unsaturated esters from the treatment of allenyl acetates, which were obtained from the reaction of organoindium in situ generated from ethyl 4-bromobutynoate and indium with aldehydes followed by acetylation, with DABCO (0.1 equiv) in DMF at room temperature. These compounds were applied to the synthesis of (*E*)-α-alkynyl-α,β-unsaturated esters through Sonogashira cross-coupling reaction.

Experimental Section

Preparation of allenyl acetate (1d). Ethyl 4-bromobutynoate (95.5 μL, 0.75 mmol) was added to a suspension of indium (57.4 mg, 0.5 mmol) and LiI (200.8 mg, 1.5 mmol) in DMF (2.0 mL). After being stirred for 30 min at room temperature under a nitrogen atmosphere, benzaldehyde (50.7 μL, 0.5 mmol) was added to reaction mixture. After 5 h, the reaction mixture was quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexane = 1:5 to give ethyl 2-(1-hydroxyphenyl)-methyl-2,3-butadienoate (93.8 mg, 86%). Pyridine (188 μL, 2.25 mmol) was added to a solution of allenyl alcohol (330 mg, 1.5 mmol) in CH_2Cl_2 (7.5 mL) at 0 °C. After being stirred for 5 min, acetyl chloride (160 μL, 2.25 mmol) was added and reaction mixture was stirred for 1 h at 0 °C. After being warmed to room temperature, the reaction mixture was quenched with 10% HCl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and combined organic layers were washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc: hexane = 1:10 to give alleny acetate (**1d**) (293.0 mg, 75%).

Typical experimental procedures for ethyl (*E*)-α-ethynylcinnamate (2d). To a solution of **1d** (131 mg, 0.5 mmol) in DMF (2.0 mL) was added DABCO (5.7 mg, 0.05 mmol) and then, reaction mixture was stirred at room temperature for 2.5 h under a nitrogen atmosphere. The reaction mixture was quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexane = 1:20 to give ethyl (*E*)-α-ethynylcinnamate (**2d**) (68.0 mg, 81%) as a pale yellow solid; mp = 38 ~ 40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.03 (m, 2H), 7.98 (s, 1H), 7.44-7.22 (m, 3H), 4.34 (q, J = 7.12 Hz, 2H), 3.57 (s, 1H), 1.31 (t, J = 7.12 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 147.9, 134.3, 131.4, 130.9, 112.6, 87.0, 79.5, 62.3, 14.7; IR (film) 3286, 2981, 1717, 1598, 1448, 1367, 1259, 1087, 1019 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{12}O_2M^+$ 200.0837, found 200.0838.

Typical experimental procedure for synthesis of ethyl (*E*)-2-phenylacetylenyl-3-phenylacrylate (3a). Et_3N (84 μL, 0.6 mmol) and iodobenzene (51 μL, 0.45 mmol) were added to a suspension of $Pd_2dba_3CHCl_3$ (6.3 mg, 2 mol %), PPh_3 (12.6 mg, 16 mol %) and CuI (5.3 mg, 10 mol %) in DMF (0.8 mL) at room temperature under nitrogen atmosphere. Then, ethyl (*E*)-2-ethynyl-3-phenylacrylate (**2d**) in DMF (0.7 mL) was added. After being stirred for 20 min at 25 °C, the reaction mixture was quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc: hexane = 1:30 to give ethyl (*E*)-2-phenylacetylenyl-3-phenylacrylate (**3a**) (65.0 mg, 80%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.06 (m, 2H), 7.94 (s, 1H), 7.56-7.53 (m, 2H), 7.46-7.40 (m, 3H), 7.39-7.34 (m, 3H), 4.36 (q, J =7.10 Hz, 2H), 1.40 (t, J = 7.10 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 145,6, 135.0, 132.0, 131.0, 130.9, 129.2, 129.0, 128.9, 123.5, 113.7, 98.5, 85.8, 62.2, 14.7; IR (film) 2980, 2202, 1718, 1260, 1198, 755, 688 cm^{-1}.

Acknowledgments. This work was supported by the KOSEF through the NRL Program funded by the MOST (No. M10600 000203-06J0000-20310), by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (2009-0087013) and by the MKE (The Ministry of Knowledge Economy), Korea, under the Leading Industry Development for Gangwon Economic Region (LIDGER) program. This work was supported by the second phase of the Brain Korea 21 Program in 2009. Dr. Sung Hong Kim at the KBSI (Daegu) is thanked for obtaining the MS data. The NMR data were obtained from the central instrumental facility in Kangwon National University.

References

1. (a) Tsuboi, S.; Kuroda, H.; Takatsuka, S.; Fukawa, T.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1986**, *58*, 5952. (b) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135. (c) Shi, W.; Xiao, F.; Wang, J. *J. Org. Chem.* **2005**, *70*, 4318. (d) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 5295. (e) Lemay, A. B.; Vulic, K. S.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 3615. (f) Tsukada, N.; Niomiya, S.; Ayoama, Y.; Inoue, Y. *Org. Lett.* **2007**, *9*, 2919.
2. (a) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini. P. *Tetrahedron* **1998**, *54*, 135. (b) Trost, B. M.; Gunzner, J. L.; Yasukata, T. *Tetrahedron Lett.* **2001**, *42*, 3775. (c) Dai, W.-M.; Wu, A.; Hamaguchi, W. *Tetrahedron Lett.* **2001**, *42*, 4211. (d) Lemay, A.; Vulic, K.; Ogilivie, W. *J. Org. Chem.* **2006**, *71*, 3615.
3. Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218.
4. (a) Forti, L.; Ghelfi, F.; Pagnoni, U. M. *Tetrahedron Lett.* **1995**, *36*, 3023. (b) Kim, K. M.; Park, I. H. *Synthesis* **2004**, 2641.
5. Kruper, W. J., Jr.; Emmons, A. H. *J. Org. Chem.* **1991**, *56*, 3323.
6. Alami, M.; Crousse, B.; Linstrumelle, G. *Tetrahedron Lett.* **1995**, *36*, 3687.
7. Buschmann, E.; Schafer, B. *Tetrahedron* **1994**, *50*, 2433.
8. (a) Satoh, T.; Itoh, N.; Onda, K.; Kitoh, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2800. (b) Ishihara, T.; Shintani, A.; Yamanaka, H. *Tetrahedron Lett.* **1998**, *39*, 4865.
9. (a) Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis* **1978**, *1*, 31. (b) Chan, T. H.; Moreland, M. *Tetrahedron Lett.* **1978**, *6*, 515. (c) Karrenbrock, F.; Schaefer, H. J. *Tetrahedron Lett.* **1979**, *31*, 2913. (d) Zapata, A.; Ferrer, G. F. *Synth. Commun.* **1986**, *16*, 1611. (e) Huang, Z.-Z.; Wu, L.-L.; Zhu, L.-S.; Huang, X. *Synth. Commun.*

1996, *26*, 677. (f) Braun, N. A.; Buerkle, U.; Feth, M. P.; Klein, I.; Spitzner, D. *Eur. J. Org. Chem.* **1998**, *8*, 1569. (g) Sano, S.; Ando, T.; Yokoyama, K.; Nagao, Y. *Synlett* **1998**, 777. (h) Tago, K.; Kogen, H. *Tetrahedron Lett.* **2000**, *56*, 8825.

10. (a) Denney, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998. (b) Yasui, S.; Nakamura, K.; Fujii, M.; Ohno, A. *J. Org. Chem.* **1985**, *50*, 3283. (c) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron Lett.* **1994**, *35*, 6913. (d) Rousseau, G.; Marie, J.-X. *Synth. Commun.* **1999**, *29*, 3705. (e) Zhang, X.; Qing, F.-L.; Yang, Y.; Yu, J.; Fu, X.-K. *Tetrahedron Lett.* **2000**, *41*, 2953. (f) Tago, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 1975. (g) Zhang, X.; Qing, F.-L.; Yu, Y. *J. Org. Chem.* **2000**, *65*, 7075. (h) Hamelin, J.; Saoudi, A.; Benhaoua, H. *Synthesis* **2003**, 2185. (i) Chang, M. Y.; Sun, P. P.; Chen, S. T.; Chang, N. C. *Tetrahedron Lett.* **2003**, *44*, 5271. (j) Olpp, T.; Brückner, R. *Synthesis* **2004**, 2135. (k) Sakamoto, R.; Murata, M.; Nishihara, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 4793.
11. (a) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3901. (b) Lee, P. H.; Lee, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 3253. (c) Lee, P. H.; Lee, K.; Kang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1139. (d) Kim, H.; Livinghouse, T.; Seomoon, D.; Lee, P. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 1127. (e) Kim, S.; Lee, K.; Seomoon, D.; Lee, P. H. *Adv. Synth. Catal.* **2007**, *349*, 2449. (f) Yu, H.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 5183. (g) Lee, K.; Lee, P. H. *Org. Lett.* **2008**, *10*, 2441. (h) Kim, S.; Lee, P. H. *Eur. J. Org. Chem.* **2008**, 2262. (i) Kim, S.; Lee, P. H. *Adv. Synth. Catal.* **2008**, *350*, 547. (j) Lee, K.; Lee, P. H. *Bull. Korean Chem. Soc.* **2008**, *29*, 487. (k) Park, C.; Lee, P. H. *Org. Lett.* **2008**, *10*, 3359. (l) Choi, Y.; Lee, P. H. *Org. Lett.* **2009**, *11*, 1445.