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Stereoselective DABCO-Catalyzed Synthesis of (*E*)-α-Ethynyl-α,*β*-Unsaturated Esters from Allenyl Acetates

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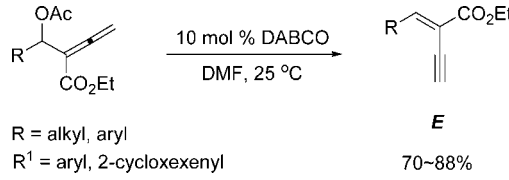
ABSTRACT



(*E*)-α-Ethynyl-α,*β*-unsaturated esters were exclusively prepared in good to excellent yields from treatment of allenyl acetates with 10 mol % DABCO in DMF at room temperature.

The construction of α-ethynyl-α,*β*-unsaturated esters is one of the challenging problems in synthetic organic chemistry.[1] In fact, many efficient synthetic methods for the preparation of these compounds have been reported for decades.[2] However, the need for a highly stereoselective synthesis of (*E*)-α-ethynyl-α,*β*-unsaturated esters has remained.[1] In general, the stereoselective 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 (Sonogashira reaction). Nevertheless, this method is limited because the stereoselective preparation of (*Z*)-α-halo-α,*β*-unsaturated esters is difficult and isomerization of these compounds somewhat occurred during the cross-coupling reactions.[3] Although a highly stereoselective synthesis of (*Z*)-α-halo-α,*β*-unsaturated esters via $CrCl_2$-mediated olefinations of aldehydes with trihaloacetates was reported,[4] the preparation of these compounds through bromination-dehydrobromination,[5] rearrangements,[6] alkoxycarbonylation,[7] deoxygenation of glycidic esters,[8] thermal eliminations,[9] or Wittig/Horner-Emmons/ Peterson-type condensations[10] often suffer from poor stereoselectivities, unsatisfactory yields, costly reagents, and/or lengthy procedures.[11] Therefore, we tried to prepare exclusively (*E*)-α-

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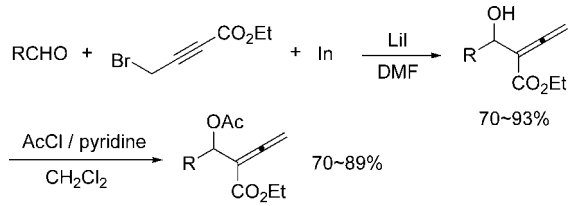
ethynyl-α,β-unsaturated esters from another precursor without the use of (*Z*)-α-halo-α,β-unsaturated esters. As part of our continuing studies into the utility of allene functional groups in synthesis,[12] we report herein the preparation of the exclusive synthesis of (*E*)-α-ethynyl-α,β-unsaturated esters from allenyl acetates catalyzed by DABCO.

First, a variety of allenyl acetates were prepared from the reaction of aldehydes with organoindium reagent in situ generated from ethyl 4-bromobutynoate and indium in the presence of lithium iodide in DMF and subsequent acetylation (Scheme 1).[12k]

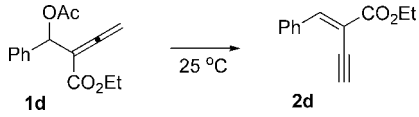
Scheme 1. Preparation of Allenyl Acetates



R = *n*-Pr, C_6H_{11}, PhCH=CBr, Ph, 4-Cl-C_6H_4, 3-Br-C_6H_4, 2-I-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

Initially, allenyl acetates were treated with a variety of acid or base. These results are summarized in Table 1.

Table 1. Reaction Optimization



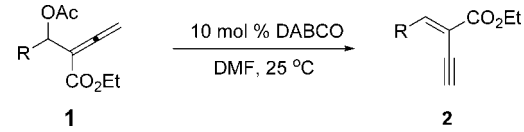
entry	reagent (equiv)	solvent	time (h)	yield (%)[a]
1	PPTS (0.2)	CH_2Cl_2	6	0
2	AcOH (0.2)	DMF	12	0
3	Pyridine (0.2)	DMF	0.67	75
4	PPh_3 (0.2)	DMF	0.5	69
5	DABCO (0.2)	DMF	0.5	75
6	DABCO (0.2)	THF	4.5	50
7	DABCO (0.20	CH_3CN	4.5	70
8	**DABCO (0.1)**	**DMF**	**2.5**	**81**
9	DABCO (2.0)	THF	0.5	54

[a] Isolated yield.

Allenyl acetate (**1d**) did not react with PPTS or 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). The *E* selectivity was determined by the chemical shift of the vinyl proton in ^{1}H NMR spectrum of the product **2d**. The vinyl proton in the *E* isomer of **2d** appeared at upfield due to the shielding effect from the ester group.[3b] Encouraged by this result, triphenylphosphine and DABCO were subsequently examined. The 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 exclusively 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 ethyl (*E*)-α-ethynyl cinnamate (**2d**) in 81% with complete stereoselectivity (entry 8). However, exposure of **1d** to DABCO (2.0 equiv) gave **2d** in 54% yield (entry 9). There is no ethyl (*Z*)-α-ethynyl cinnamate formed in any reactions. In addition, the corresponding allenyl alcohol did not react with DABCO.

To demonstrate the efficiency and scope of the present method, we applied the catalytic system to a variety of allenyl acetates (Table 2). Allenyl acetate **1a** was treated with

Table 2. DABCO-Catalyzed Synthesis of (*E*)-α-Ethynyl-α,β-Unsaturated Esters from Allenyl Esters



1 **2**

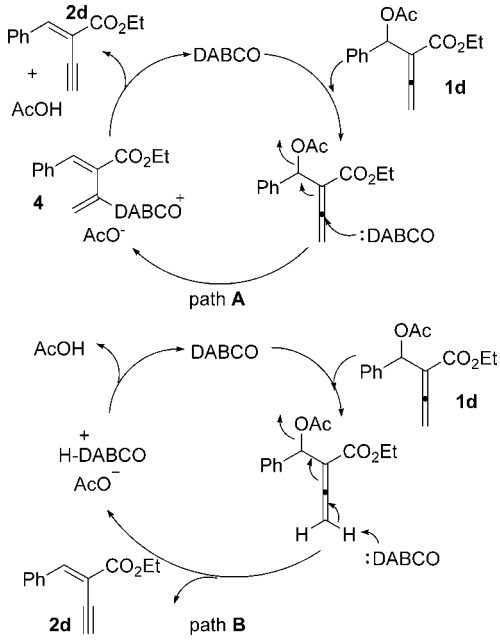
entry	R	reactant (**1**)	time (h)	product (**2**)	yield (%)[a]
1	*n*-Pr	**1a**	3.5	**2a**	72
2	C_6H_{11}	**1b**	4	**2b**	82
3	PhCH=CBr	**1c**	1	**2c**	70
4	Ph	**1d**	2.5	**2d**	81
5	4-Cl−C_6H_4	**1e**	0.5	**2e**	86
6	3-Br−C_6H_4	**1f**	0.5	**2f**	88
7	2-I−C_6H_4	**1g**	1	**2**g	73
8	2,4,6-Me_3−C_6H_2	**1h**	3	**2h**	84
9	3-MeO−C_6H_4	**1i**	2	**2**i	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] Isolated yield.

DABCO (0.1 equiv) in DMF for 3.5 h to selectively produce 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 exclusively produced in 82% yield (entry 2). Under the optimum reaction conditions, allenyl acetate **1c** prepared from *trans*-2-bromocinnamaldehyde 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 5−12). 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 good to excellent yields (entries 5−7). Treatment of

allenyl acetates having 2,4,6-trimethylphenyl and 3,5-dimethoxyphenyl group with DABCO (0.1 equiv) exclusively provided (*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 even though the derivatives of allenyl acetate (**1l** and **1m**) bearing electron-withdrawing groups such as ketone and ester 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 could not be prepared because acetylation of the corresponding 3°-alcohol did not proceed.

Scheme 2. Plausible Reaction Pathway



One possible reaction mechanism is shown in path **A** of Scheme 2. S_N 2′-type displacement of allenyl acetate with DABCO affords the vinylammonium salt **4** as an intermediate. Subsequent elimination reaction of **4** produces (*E*)-α-ethynyl-α,*β*-unsaturated esters **2d** and regenerates the DABCO catalyst to continue catalytic cycle. Displacement of allenyl acetate through abstract of allenyl proton by DABCO can be postulated as another possible mechanism of the reaction in path **B**.[13]However, the latter mechanism is ruled out because the vinylammonium salt **4** is detected in NMR study. ^{1}H NMR (400 MHz, DMF-d_7, 25 °C) study of the reaction mixture of **1d** and DABCO showed new vinylic signals at δ 6.67 (d, J = 3.98 Hz, 1H) and δ 6.16 (d, J = 3.94 Hz, 1H), indicating that α-ethynyl-α,*β*-unsaturated ester **2d** are produced through the vinylammonium salt as intermediate (Figure 1).

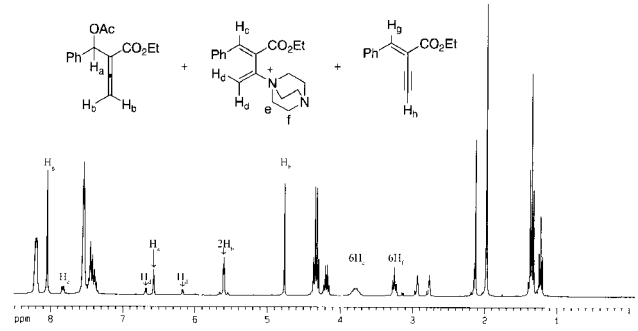
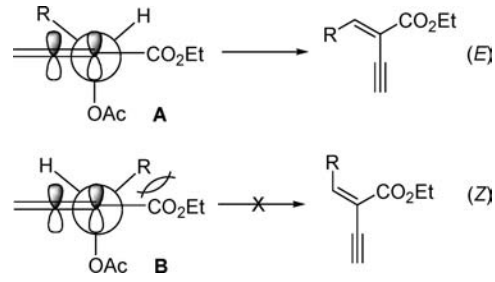


Figure 1. ^{1}H NMR (300 MHz, DMF-d_7, 25 °C) spectrum of the reaction mixture of **1d** and DABCO.

A piece of mechanistic evidence involves the exclusive formation of (*E*)-α-ethynyl-α,*β*-unsaturated esters. The appropriate overlap to expel the acetate group requires overlap of the π-system with the antibonding orbital of the C-OAc bond as it reacts with DABCO. Then, the two appropriate conformations (**A** and **B**) are possible. The conformation **A** should be preferred due to a simple steric argument (Scheme 3).

Scheme 3. Reason of Exclusive Formation of (*E*)-α-Ethynyl-α,*β*-Unsaturated Esters



In summary, we have developed an exclusive synthetic method of (*E*)-α-ethynyl-α,*β*-unsaturated esters from the treatment of allenyl acetates with DABCO (0.1 equiv) in DMF at room temperature.

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

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