Pergamon

Tetrahedron Letters 40 (1999) 5019–5022

TETRAHEDRON LETTERS

Facile Stereoselective Syntheses of (*E*)- and (*Z*)-α-Substituted Cinnamates by Stereoselective Dehydration Reaction with 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)

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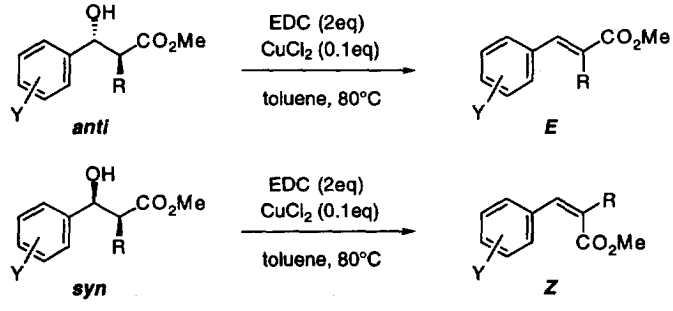
Received 9 March 1999; revised 23 April 1999; accepted 30 April 1999

Abstract: Highly stereoselective syntheses of (*E*)- and (*Z*)-α-substituted cinnamates have been achieved by dehydration reaction of *anti*- and *syn*-α-substituted-β-hydroxyphenylpropionates with EDC in good yields. This facile method has been applied to the stereoselective syntheses of (*E*)- and (*Z*)-α-alkylidene-γ-butyrolactones.

As a part of our program at development of an antithrombotic agent having a diarylidene succinate structure, we needed a facile and stereoselective method for the synthesis of (*E*)- and (*Z*)-α-substituted cinnamates.[1] The synthetic method to be most easily hit upon is the E2 elimination reaction of the corresponding *syn*- and *anti*-β-hydroxyesters. Indeed, the (*E*)-α-substituted cinnamates were obtained stereoselectively in high yield from corresponding *syn*-β-hydroxyesters by E2 elimination reaction. However, the (*Z*)-α-substituted cinnamates were not obtained stereoselectively from corresponding *anti*-β-hydroxyesters.[2] In order to solve this problem, two methods based on the Honer-Emmons reaction[5,6] and the reductive elimination reaction of the *syn*-β-hydroxy-α-phenylthioester have been reported.[7,8] However, these methods have the defects such as using expensive and difficultly accessible reagents and limitation in the substituents on the α-position. We report herein a facile method for the stereoselective synthesis of (*E*)- and (*Z*)-α-substituted cinnamate based on the stereoselective dehydration of the easily accessible *anti*- and *syn*-α-substituted-β-hydroxyphenylpropionate by ethyldimethylaminopropylcarbodiimide (EDC) (Scheme 1).



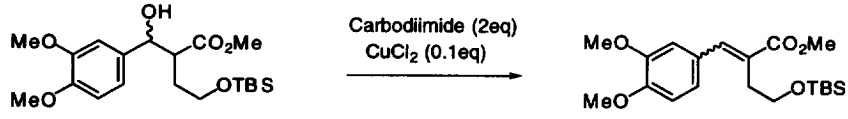
Scheme 1

PII: S0040-4039(99)00923-5

E. J. Corey and his co-worker have reported that the (*E*)- and (*Z*)-α-alkylidene-γ-butyrolactones were stereoselectively synthesized by the dehydration reaction of the corresponding *anti* - and *syn*-aldols derived from γ-butyrolactone with dicyclohexylcarbodiimide (DCC).[9] Thus, we examined the dehydration reaction of the *anti*- and *syn*-β-hydroxyesters **1** and **2** with DCC under the same reaction conditions in the first stage of our study. Although the *anti*-β-hydroxyester **2** gave the (*E*)-cinnamate **4** selectively, the *syn*-β-hydroxyester **1** did not give the cinnamate but the *anti*-β-hydroxyester **2**[10] (Entries 1 and 2). The reaction in toluene at 80°C gave the eliminated product, which was, however, a mixture of the (*E*) and (*Z*)-isomers (Entry 3). Because the obtained (*Z*)-isomer did not isomerize to the (*E*)-isomer under the reaction conditions,[11] this result indicated that the conversion of the *syn*-β-hydroxyester **1** into the *anti*-β-hydroxyester **2** took place firstly and then the elimination reaction proceeded to bring about the (*E*)-cinnamate **4**.

We considered that the desired (*Z*)-cinnamate **3** would be selectively obtained if we could find out an appropriate carbodiimide which promotes the elimination reaction to proceed sufficiently faster than the isomerization reaction. Because a carbodiimide being sterically less hindered than DCC would be envisaged to

Table 1. Dehydration Reaction of **1** or **2** with Carbodiimide and $CuCl_2$



***syn* (1) or *anti* (2)** → **Z (3) or E (4)**

Entry	Substrate	Carbodiimide	Solvent	Temperature	Time	Yield[a]	Z : E[b]
1	*syn* (1)	DCC	Et_2O	35°C	24h	trace[c]	
2	*anti* (2)	DCC	Et_2O	35°C	24h	52%	1 : >99
3	*syn* (1)	DCC	toluene	80°C	2h	45%	33 : 67
4	*anti* (2)	DCC	toluene	80°C	2h	73%	1 : >99
5	*syn* (1)	DIPC	toluene	80°C	2h	41%	44 : 56
6	*syn* (1)	EDC	toluene	80°C	2h	95%	96 : 4
7	*anti* (2)	EDC	toluene	80°C	2h	95%	1 : >99
8	*syn* (1)	EDC	toluene	25°C	96h	45%	88 : 12
9	*syn* (1)	EDC	toluene	50°C	16h	69%	92 : 8
10	*syn* (1)	EDC	toluene	100°C	2h	94%	95 : 5
11	*syn* (1)	EDC	Et_2O	35°C	30h	21%	86 : 14
12	*syn* (1)	EDC	CH_2Cl_2	40°C	30h	50%	78 : 22
13	*syn* (1)	EDC	dioxane	80°C	2h	38%	85 : 15
14	*syn* (1)	EDC	THF	65°C	2h	46%	81 : 19
15	*syn* (1)	EDC	CH_3CN	80°C	2h	57%	71 : 29
16	*syn* (1)	EDC	DMF	80°C	2h	8%	70 : 30

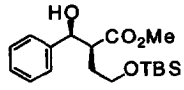
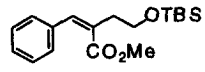
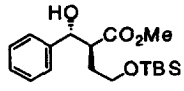
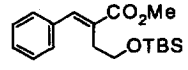
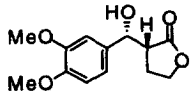
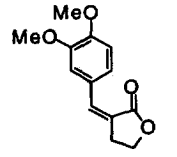
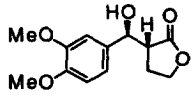
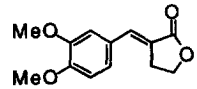
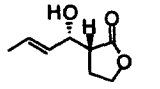
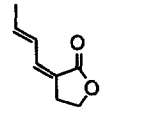
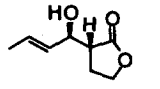
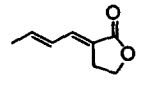
[a] Isolated yields. [b] The ratio was determined by 200 MHz ^{1}H-NMR. [c] *anti*-β-Hydroxyester (**2**) was isolated in 23% yield and *syn*-β-hydroxyester (**1**) was recovered (30%).

meet the requirement, we next examined the reaction in the presence of diisopropylcarbodiimide (DIPC) and EDC. Indeed, DIPC improved the yield of the (Z)-cinnamate **3**, but it was not yet satisfactory (Entry 5). However, the desired (Z)-cinnamate **3** was expectedly obtained selectively in a good yield, when **1** was treated with EDC in toluene at 80 ℃ for 2 hr (Entry 6). Whereas the elimination reaction of **2** in the use of EDC gave **4** in a higher yield than that in the use of DCC (Entry 7).

With these promising results, we next examined the optimal reaction conditions. The reaction was examined in toluene at 25 ℃, 50 ℃, 80 ℃ and 100 ℃. At the low temperatures (25 ℃ and 50 ℃), the reaction took rather long period to complete, and both yield and selectivity lowered than those at 80 ℃ (Entries 6,8 and 9). Almost the same yield was achieved when the reaction was carried out in toluene at 100 ℃ (Entry 10). The reation was also examined in various solvents at 80 ℃ or under the refluxing conditions. However, these other solvents brought about only results inferior to that in toluene in terms of yield and selectivity (Entries 11-16). Thus, the reaction revealed to proceed optimally in toluene at 80 ℃ for 2h.

In order to clarify the scope and limitation of the present method, a variety of *anti-* and *syn*-β-hydroxyesters and lactones were subjected to the reaction (Table 2). In the use of EDC, the reaction

Table 2. Stereoselective Synthesis of Cinnamate and Alkylidene-γ-butyrolactone with EDC and $CuCl_2$

Entry	Substrate	Carbodiimide	Product	Yield[a] (*Z* : *E*)[b]
1		EDC		60% (86 : 14)
2		EDC (100°C)		99% (>99 : 1)
3		DCC		32% (25 : 75)
4		EDC		99% (1 : >99)
5		EDC		78% (80 : 20)
6		DCC		55% (32 : 68)
7		EDC		96% (1 : >99)
8		EDC		62% (94 : 6)
9		DCC		49% (22 : 78)
10		EDC		62% (1 : >99)

Unless otherwise noted, reactions were carried out using carbodiimide (2eq) and $CuCl_2$ (0.1eq) in toluene at 80°C for 2h. [a] Isolated yields. [b] The ratio was determined by 200 MHz ^{1}H-NMR.

proceeded stereoselectively to give the corresponding (*E*)- and (*Z*)-α-substituted cinnamates, and the (*E*)- and (*Z*)-α-alkylidene-γ-butyrolactones were obtained stereoselectively in moderate to good yields. In all cases, EDC was superior to DCC. In the case that the good result was not obtained at 80℃, the yield and the stereoselectivity were improved under the high temperature conditions (Entry 2).

As described above, a highly stereoselective method for the syntheses of the (*E*)- and (*Z*)-α-substituted cinnamates and the (*E*)- and (*Z*)-α-alkylidene-γ-butyrolactones was developed. It is noteworthy that the (*Z*)-α-substituted cinnamates and the (*Z*)-α-alkylidene-γ-butyrolactones, which are hitherto difficult to be obtained, can be stereoselectively synthesized in good yields. The mechanism of the reaction providing the high selectivity is under investigation and will be reported elsewhere.

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2. The methanesulfonate of the *syn*-α-substituted-β-hydroxyphenylpropionate **1** was treated with DBU to afford the (*E*)-α-substituted cinnamate **4** stereoselectively in 97% yield as a sole product. However, the corresponding *anti*-methanesulfonate afforded a mixture of (*E*)- and (*Z*)-α-substituted cinnamates (68:32) in 98% yield under the same reaction conditions probably due to the E1cB elimination reaction which proceeded competitively with E2 elimination reaction. The α-proton of the β-hydroxyester seems acidic enough for the E2 elimination reaction to compete with the E1cB elimination reaction. Similar results have been reported in the synthesis of the α-benzylidene-γ-butyrolactones[3] and the α-benzylideneketones.[4]
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11. The *Z*-isomer was treated with EDC and $CuCl_2$ in toluene at 80 °C, and *E*-isomer was not obtained at all.
12. The typical procedures are as followings. A solution of β-hydroxyester (0.25 mmol) in toluene (10 ml) was treated with EDC (0.5 mmol) and $CuCl_2$ (0.025 mmol) at 80 ℃ for 2 h. The reaction mixture was quenched with water and the mixture was extracted with AcOEt . The organic layer was washed with aqueous citric acid, aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. After determining the Z/E ratio of the crude mixture, by 200 MHz ^{1}H-NMR, the product was purified by silica gel column chromatography.