

A Microwave-assisted Deconjugative Esterification of α,β -Unsaturated Carboxylic Acids through α,β -Unsaturated Ketene Intermediates

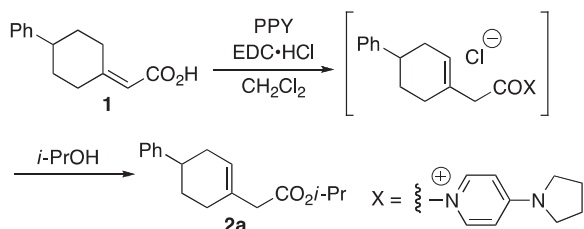
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A facile synthetic approach to β,γ -unsaturated esters by deconjugative esterification of α,β -unsaturated carboxylic acids with alcohols in the presence of 1,3-dicyclohexylcarbodiimide (DCC), $\text{Me}_3\text{N}\cdot\text{HCl}$, and Me_2NEt is described. The one-pot synthesis was effectively improved under microwave irradiation.

β,γ -Unsaturated esters are among the most important building blocks in organic chemistry.¹ Therefore, considerable efforts have been made to develop an efficient method for synthesizing β,γ -unsaturated esters. The deconjugation of α,β -unsaturated compounds, such as photochemical deconjugation,² alkylative deconjugation,³ and anionic deconjugation,⁴ represents one of the most useful strategies. Nevertheless, only a few reports have been published on deconjugative esterification⁵ and amidation⁶ of α,β -unsaturated carboxylic acids. As part of our work in this area, we have already developed deconjugative esterification and amidation of 2-cyclohexylideneacetic acids, such as **1** through β,γ -unsaturated acyl pyridinium intermediates in the presence of a catalytic amount of 4-(pyrrolidin-1-yl)-pyridine (PPY) as depicted in Scheme 1.⁷ The following describes an outcome of our efforts to synthesize β,γ -unsaturated esters by a microwave-assisted deconjugative esterification of α,β -unsaturated carboxylic acids through α,β -unsaturated ketene intermediates.

The formation of ketenes from acid chlorides and tertiary amines is an ordinary reaction. However, there have been only a few reports on the preparation of α,β -unsaturated ketenes by dehydrochlorination of the corresponding acid chlorides.⁸ On the other hand, Olah et al. reported the synthesis of stable dialkyl ketenes involving intramolecular dehydration of the corresponding carboxylic acids with 1,3-dicyclohexylcarbodiimide (DCC) in the presence of catalytic amounts of Et_3N .⁹ Thus, we first applied our synthetic method to the deconjugative esterification of 2-cyclohexylideneacetic acid **1** with an equimolar amount of DCC in the presence of a catalytic amount of Et_3N in Et_2O or CH_2Cl_2 , followed by treatment with excess amounts of *i*-PrOH. However, β,γ -unsaturated ester **2a** was not obtained at all.

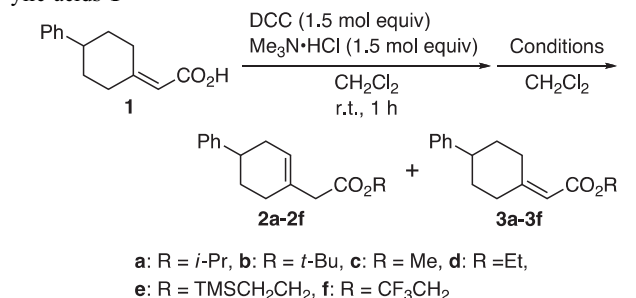


Scheme 1. Deconjugative esterification of 2-cyclohexylideneacetic acid **1** through an acyl pyridinium intermediate.

After a preliminary investigation of the effect of a tertiary amine on deconjugative esterification, we found a combination of excess amounts of $\text{Me}_3\text{N}\cdot\text{HCl}$ and Me_2NEt , instead of a catalytic amount of Et_3N , to be efficient (Table 1, Entries 1–3).¹⁰ Thus, DCC and $\text{Me}_3\text{N}\cdot\text{HCl}$ were added to carboxylic acid **1** in CH_2Cl_2 , then the treatment with Me_2NEt and *i*-PrOH afforded a mixture of β,γ -unsaturated ester **2a** and α,β -unsaturated ester **3a** with a **2a:3a** ratio of 97:3, and in 85% yield. In the reaction with *t*-BuOH, the yield was found to be somewhat lower (57%), but the corresponding β,γ -unsaturated ester **2b** was obtained as the sole product (**2b:3b** = 100:0). On the other hand, **2c** and **3c** were obtained with a low regioselectivity (**2c:3c** = 42:58) in the reaction with MeOH. Under similar conditions, the deconjugative esterification of carboxylic acid **4** with *i*-PrOH and *t*-BuOH gave **7a** and **7b** as major products, respectively (Table 2, Entries 1 and 2).

To improve the reaction yields and shorten the reaction times, several experiments were conducted by elevating the reaction temperature. This revealed that carboxylic acid **1** gave

Table 1. Deconjugative esterification of α,β -unsaturated carboxylic acids **1**



Entry	R	Conditions ^a	Yield/% ^b	2:3 ^c
1	<i>i</i> -Pr	A	85	97:3 (2a:3a)
2	<i>t</i> -Bu	A	57	100:0 (2b:3b)
3	Me	A	81	42:58 (2c:3c)
4	<i>i</i> -Pr	B	86	98:2 (2a:3a)
5	<i>t</i> -Bu	B	79	98:2 (2b:3b)
6	Me	B	91	78:22 (2c:3c)
7	Et	B	86	94:6 (2d:3d)
8	TMSCH ₂ CH ₂	B	86	94:6 (2e:3e)
9	CF ₃ CH ₂	B	91	69:31 (2f:3f) ^d
10	<i>i</i> -Pr	C	35	34:66 (2a:3a)
11	<i>i</i> -Pr	B ^e	26	98:2 (2a:3a)

^aA: 50 °C, 12–21 h, **1**/ Me_2NEt /ROH (1:7.5:5); B: MW (90 °C), 10 min, **1**/ Me_2NEt /ROH (1:3:1.5); C: MW (90 °C), 10 min, **1**/ Me_2NEt /ROH (1:0:1.5). ^bIsolated yields. ^cDetermined by ¹H NMR (400 MHz, benzene-*d*₆) analysis of the crude esters. ^dThe ratios of **2f:3f** were varied from 66:34 to 73:27 on repeated run. ^e $\text{Me}_3\text{N}\cdot\text{HCl}$ was not added.

Table 2. Deconjugative esterification of α,β -unsaturated carboxylic acids **4–6**

$\text{Ph}-\text{CH}(\text{R}^1)-\text{CH}(\text{R}^2)-\text{CO}_2\text{H} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{r.t., 1 h}]{\text{DCC (1.5 mol equiv), Me}_3\text{N}\cdot\text{HCl (1.5 mol equiv)}} \text{7-9} + \text{(E)-10-12} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{MW (90 }^\circ\text{C, 10 min)}]{\text{Me}_2\text{NEt (3 mol equiv), ROH (1.5 mol equiv)}} \text{7-9} + \text{(E)-10-12}$					
4,7,10: $\text{R}^1 = \text{R}^2 = \text{H}$, 5,8,11: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, 6,9,12: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$ a: $\text{R} = i\text{-Pr}$, b: $\text{R} = t\text{-Bu}$, c: $\text{R} = \text{Me}$					
Entry	R^1	R^2	R	Yield/% ^b	7-9:(E)-10-12^c
1 ^a	H	H	<i>i</i> -Pr	72	91:9 [7a:(E)-10a]
2 ^a	H	H	<i>t</i> -Bu	48	100:0 [7b:(E)-10b]
3 ^a	H	H	Me	72	18:82 [7c:(E)-10c]
4	H	H	<i>i</i> -Pr	74	94:6 [7a:(E)-10a]
5	H	H	<i>t</i> -Bu	73	99:1 [7b:(E)-10b]
6	H	Me	<i>i</i> -Pr	79	86:14 [8a:(E)-11a]
7	H	Me	<i>t</i> -Bu	64	100:0 [8b:(E)-11b]
8	Me	H	<i>i</i> -Pr	16	99:1 [9a:(E)-12a]
9	Me	H	<i>t</i> -Bu	7	100:0 [9b:(E)-12b]

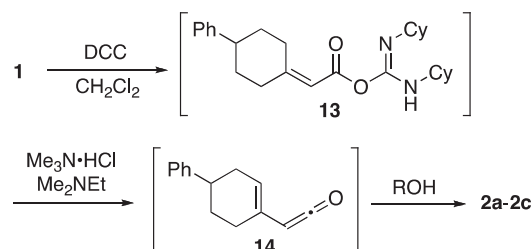
^a50 °C, 18 h, (E)-4/Me₂NEt/ROH (1:7.5:5). ^bIsolated yields.^cDetermined by ¹H NMR (400 MHz, benzene-*d*₆) analysis of the crude esters.

2a with high regioselectivity at 90 °C for only 10 min utilizing a Biotage Initiator[®] microwave synthesizer (Table 1, Entries 4–9).¹¹ In addition, it was proven that microwave irradiation could reduce the amounts of the reagents, Me₂NEt and *i*-PrOH. On the other hand, low yields were observed in the absence of Me₃N·HCl or Me₂NEt (Table 1, Entries 10 and 11).

To investigate the scope and limitations of this procedure, α,β -unsaturated carboxylic acids (E)-**4–6** were subjected to microwave-assisted deconjugative esterification. The results are shown in Table 2. These reactions also gave the corresponding β,γ -unsaturated esters **7a–7c**, **8a** and **8b** (E/Z = 45:55–50:50) as major products, except for carboxylic acids (E)-**6** (Table 2, Entries 8 and 9). In the case of (E)-**6**, steric hindrance may reduce the yields of (E)-**9a** and -**9b**. In addition, the deconjugative esterification of (Z)-**6** with *i*-PrOH and *t*-BuOH afforded (E)-**9a** and -**9b** with **9:12** ratios of 100:0, and in 19% and 7% yields, respectively. On the other hand, (Z)-**4** gave **7a** and **7b** (E/Z = 50:50) with **7:(E)-10** ratios of 96:4 and 100:0, and in 78% and 72% yields under the same reaction conditions.

As a mechanism, we propose an initial formation of *O*-acylurea **13**, which leads to α,β -unsaturated ketene intermediate **14** as shown in Scheme 2. β,γ -Unsaturated ester **2** should be obtained by the esterification of unsaturated ketene **14** with alcohols. Direct esterification of *O*-acylurea **13** may afford α,β -unsaturated ester **3** as minor products. Although the detailed reaction mechanism remains obscure, free Me₃N, which might be furnished by HCl exchange with Me₂NEt during the reaction, seems to be important in the deprotonation of one of the γ -protons.

In conclusion, we have presented a method for obtaining β,γ -unsaturated esters **2**, **7**, and **8** from α,β -unsaturated

**Scheme 2.** Deconjugative esterification of 2-cyclohexylideneacetic acid **1** through an α,β -unsaturated ketene intermediate.

carboxylic acids **1**, **4**, and **5** in an efficient microwave-assisted deconjugative esterification. Efforts toward the deconjugative esterification of optically active 2-cyclohexylideneacetic acids with an axis of chirality through an unsaturated ketene intermediate are ongoing in our laboratories, and the results of these investigations will be reported in due course.

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- 10 Effects of a combination of reagents, such as Me₃N·HCl/Me₂NEt, Me₃N·HCl/Et₃N, Me₃N·HCl/*i*-Pr₂NEt, Me₃N·HCl/DBU, Me₃N·HCl/TMG, Et₃N·HCl/Me₂NEt, Et₃N·HCl/Et₃N, etc., were investigated.
- 11 A typical procedure was as follows. To a solution of 2-(4-phenylcyclohexylidene)acetic acid (**1**) (65 mg, 0.30 mmol) in anhydrous CH₂Cl₂ (0.75 mL) in a Biotage vial of 0.5–2.0 mL were added DCC (93 mg, 0.45 mmol) and Me₃N·HCl (43 mg, 0.45 mmol). The mixture was stirred at room temperature for 1 h, and then Me₂NEt (97 μ L, 0.90 mmol) and *i*-PrOH (34 μ L, 0.45 mmol) were added to the solution. The vial was sealed and then irradiated at 90 °C for 10 min. The reaction mixture was then filtered and concentrated in vacuo. The oily residue (**2a:3a** = 98:2) was purified by silica gel (Kanto Chemical 60N) column chromatography [*n*-hexane–AcOEt (40:1)] to afford the mixture of **2a** and **3a** (67 mg, 86% yield) as a colorless oil.