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

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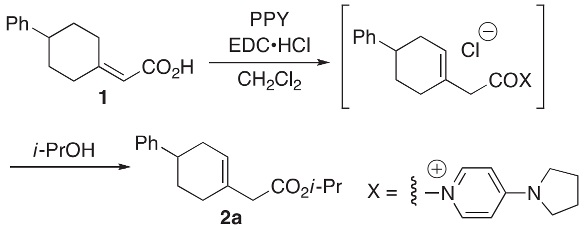
A facile synthetic approach to β,γ-unsaturated esters by deconjugative esterification of α,β-unsaturated carboxylic acids with alcohols in the presence of 1,3-dicyclohexylcarbodiimide (DCC), $Me_3N{\cdot}HCl$, and Me_2NEt is described. The one-pot synthesis was effectively improved under microwave irradiation.

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 esterification[5] and amidation[6] 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.

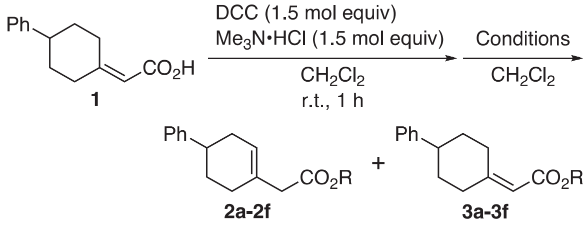


Scheme 1. Deconjugative esterification of 2-cyclohexylideneacetic acid **1** through an acyl pyridinium intermediate.

After a preliminary investigation of the effect of a tertiary amine on deconjugative esterification, we found a combination of excess amounts of $Me_3N{\cdot}HCl$ and Me_2NEt, instead of a catalytic amount of Et_3N, to be efficient (Table 1, Entries 1–3).[10] Thus, DCC and $Me_3N{\cdot}HCl$ 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**

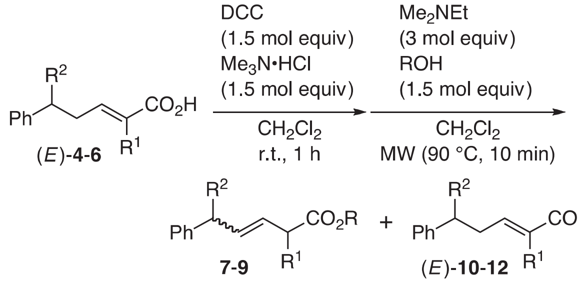


a: R = *i*-Pr, **b**: R = *t*-Bu, **c**: R = Me, **d**: R = Et,
e: R = $TMSCH_2CH_2$, **f**: R = CF_3CH_2

Entry	R	Conditions[a]	Yield/%[b]	2:3[c]
1	*i*-Pr	A	85	97:3 (**2a**:**3a**)
2	*t*-Bu	A	57	100:0 (**2b**:**3b**)
3	Me	A	81	42:58 (**2c**:**3c**)
4	*i*-Pr	B	86	98:2 (**2a**:**3a**)
5	*t*-Bu	B	79	98:2 (**2b**:**3b**)
6	Me	B	91	78:22 (**2c**:**3c**)
7	Et	B	86	94:6 (**2d**:**3d**)
8	$TMSCH_2CH_2$	B	86	94:6 (**2e**:**3e**)
9	CF_3CH_2	B	91	69:31 (**2f**:**3f**)[d]
10	*i*-Pr	C	35	34:66 (**2a**:**3a**)
11	*i*-Pr	B[e]	26	98:2 (**2a**:**3a**)

[a] A: 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). [b] Isolated yields. [c] Determined by ^1H NMR (400 MHz, benzene-d_6) analysis of the crude esters. [d] The ratios of **2f**:**3f** were varied from 66:34 to 73:27 on repeated run. [e] $Me_3N{\cdot}HCl$ was not added.

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



4,**7**,**10**: R^1 = R^2 = H, **5**,**8**,**11**: R^1 = H, R^2 = Me, **6**,**9**,**12**: R^1 = Me, R^2 = H
a: R = *i*-Pr, **b**: R = *t*-Bu, **c**: R = Me

Entry	R^1	R^2	R	Yield/%[b]	**7**–**9**:(*E*)-**10**–**12**[c]
1[a]	H	H	*i*-Pr	72	91:9 [**7a**:(*E*)-**10a**]
2[a]	H	H	*t*-Bu	48	100:0 [**7b**:(*E*)-**10b**]
3[a]	H	H	Me	72	18:82 [**7c**:(*E*)-**10c**]
4	H	H	*i*-Pr	74	94:6 [**7a**:(*E*)-**10a**]
5	H	H	*t*-Bu	73	99:1 [**7b**:(*E*)-**10b**]
6	H	Me	*i*-Pr	79	86:14 [**8a**:(*E*)-**11a**]
7	H	Me	*t*-Bu	64	100:0 [**8b**:(*E*)-**11b**]
8	Me	H	*i*-Pr	16	99:1 [**9a**:(*E*)-**12a**]
9	Me	H	*t*-Bu	7	100:0 [**9b**:(*E*)-**12b**]

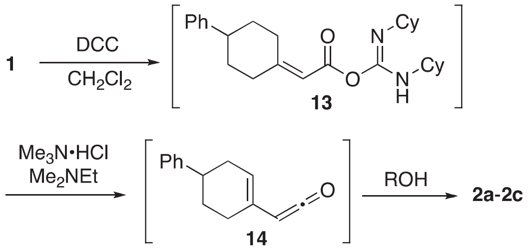
[a] 50 °C, 18 h, (*E*)-**4**/Me$_2$NEt/ROH (1:7.5:5). [b] Isolated yields. [c] Determined by ^{1}H NMR (400 MHz, benzene-d_6) analysis of the crude esters.

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, Me$_2$NEt and *i*-PrOH. On the other hand, low yields were observed in the absence of Me$_3$N•HCl or Me$_2$NEt (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 Me$_3$N, which might be furnished by HCl exchange with Me$_2$NEt 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 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.



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

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10 Effects of a combination of reagents, such as Me$_3$N•HCl/Me$_2$NEt, Me$_3$N•HCl/Et$_3$N, Me$_3$N•HCl/*i*-Pr$_2$NEt, Me$_3$N•HCl/DBU, Me$_3$N•HCl/TMG, Et$_3$N•HCl/Me$_2$NEt, Et$_3$N•HCl/Et$_3$N, 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 CH$_2$Cl$_2$ (0.75 mL) in a Biotage vial of 0.5–2.0 mL were added DCC (93 mg, 0.45 mmol) and Me$_3$N•HCl (43 mg, 0.45 mmol). The mixture was stirred at room temperature for 1 h, and then Me$_2$NEt (97 µL, 0.90 mmol) and *i*-PrOH (34 µL, 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.