Novel Deconjugative Esterification of 2-Cyclohexylideneacetic Acids through 4-(Pyrrolidin-1-yl)pyridine-catalyzed Carbodiimide Couplings

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4-(Pyrrolidin-1-yl)pyridine-catalyzed deconjugative esterification of 2-cyclohexylideneacetic acids afforded isopropyl 2-(cyclohex-1-enyl)acetate by employing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride as a coupling reagent. On the other hand, 4-(pyrrolidin-1-yl)pyridine-catalyzed esterification with 1,3-dicyclohexylcarbodiimide was not accompanied by deconjugation and gave isopropyl 2-cyclohexylideneacetate.

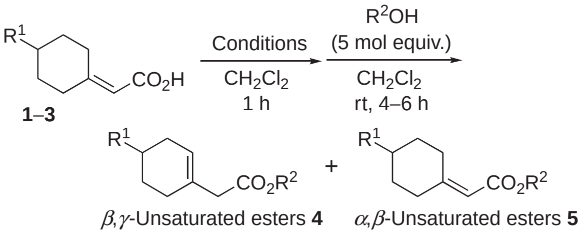
β,γ-Unsaturated esters are of interest as synthetic building blocks in organic chemistry and medicinal chemistry. There are numerous deconjugative reactions of α,β-unsaturated esters, such as photochemical deconjugation,[1] alkylative deconjugation,[2] and anionic deconjugation.[3] However, conventional esterification of carboxylic acids with alcohols utilizing carbodiimide reagents has received little attention as a deconjugative reaction.[4] Here, we describe the 4-(pyrrolidin-1-yl)pyridine (PPY)[5]-catalyzed deconjugative esterification of 2-cyclohexylideneacetic acids **1**–**3** achieved by employing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl)[6] as a coupling reagent.

We have found that an esterification of 2-(4-phenylcyclohexylidene)acetic acid (**1**) and *i*-PrOH through PPY-catalyzed EDC•HCl coupling in CH_2Cl_2 at room temperature afforded β,γ-unsaturated ester **4a** with a **4a**:**5a** ratio of 96:4, and in 74% yield (Table 1, Entry 1).[7] The tendency toward deconjugation in the esterification seemed to depend on the bulkiness of alcohols. The esterification of carboxylic acid **1** with MeOH and EtOH resulted in a low regioselectivity (**4**:**5** = 62:38) (Table 1, Entries 2 and 3). In the reaction with *t*-BuOH, the regioselective esterification suffered from low yield (Table 1, Entry 4). Under similar conditions, carboxylic acids **2** and **3** afforded β,γ-unsaturated esters **4e** and **4f** with high regioselectivities (Table 1, Entries 5 and 6). On the other hand, when 1,3-dicyclohexylcarbodiimide (DCC)[8] or EDC was used instead of EDC•HCl, α,β-unsaturated ester **5a** was obtained as the major product (**4a**:**5a** = 12:88 or 24:76) (Table 1, Entries 7 and 8). This suggested the significance of a tertiary amine hydrochloride moiety of EDC•HCl for deconjugative esterification. Hence, trimethylamine hydrochloride was added to the PPY-catalyzed reaction utilizing DCC as a coupling reagent to alter the regioselectivity. The major product of this was β,γ-unsaturated ester **4a** (**4a**:**5a** = 93:7) (Table 1, Entry 9). Ordinary PPY-catalyzed esterification of carboxylic acids **1**–**3** and *i*-PrOH with DCC, which was not accompanied by deconjugation, were carried out within a range of **4**:**5** ratios of 11:89–4:96 (Table 1, Entries 10–12). The **4**:**5** ratios were determined by ^{1}H NMR analysis (400 MHz, C_6D_6).

Next, we attempted amidation of carboxylic acid **1** with several amines under conditions similar to those of deconjugative esterification. The amidation of carboxylic acid **1** with $BnNH_2$ and $PhNH_2$ afforded β,γ-unsaturated amides **6a** and **6b** with modest regioselectivity (Table 2, Entries 1 and 2). On the other hand, treatment of **1** and 4-nitroaniline (4-$NO_2C_6H_4$-NH_2) with PPY and EDC•HCl in CH_2Cl_2 at room temperature afforded β,γ-unsaturated amide **6c** as the sole product (Table 2, Entry 3). The regioselectivity in the amidation of carboxylic acid **1** seemed to vary depending on the pK_{aH} value of each amine ($BnNH_2$: 9.34, $PhNH_2$: 4.87, 4-$NO_2C_6H_4NH_2$: 1.02).[9] The amidation of **1** and $BnNH_2$ or $PhNH_2$ without employing PPY afforded α,β-unsaturated amides **7a** and **7b**, though in low yields. It is worth noting that these reactions were not accompanied by any deconjugation (Table 2, Entries 4 and 5).

In conclusion, we demonstrated a novel deconjugative esterification of 2-cyclohexylideneacetic acids **1**–**3** catalyzed by PPY employing EDC•HCl as a coupling reagent. Although the mechanism underlying this reaction is not clear at this stage, the reaction probably involves the equilibrium between the active PPY-intermediates, β,γ-unsaturated acyl pyridinium and α,β-unsaturated acyl pyridinium, as shown in Scheme 1.

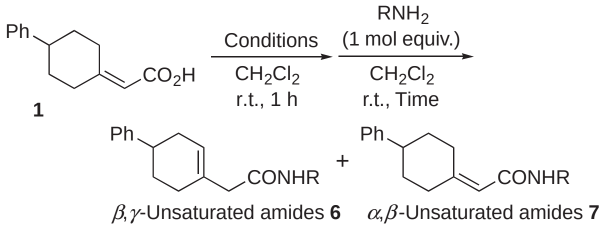
Table 1. Deconjugative esterification of 2-cyclohexylideneacetic acids **1**–**3**



Entry	R^1	R^2	Conditions[a]	Yield/%[b]	**4**:**5**[c]	
1	Ph	*i*-Pr	A	74	96:4	(**4a**:**5a**)
2	Ph	Me	A	83	62:38	(**4b**:**5b**)
3	Ph	Et	A	73	62:38	(**4c**:**5c**)
4	Ph	*t*-Bu	A	5	97:3	(**4d**:**5d**)
5	Me	*i*-Pr	A	79	92:8	(**4e**:**5e**)
6	*t*-Bu	*i*-Pr	A	79	93:7	(**4f**:**5f**)
7	Ph	*i*-Pr	B	59	12:88	(**4a**:**5a**)
8	Ph	*i*-Pr	C	36	24:76	(**4a**:**5a**)
9	Ph	*i*-Pr	B[d]	53	93:7	(**4a**:**5a**)
10	Ph	*i*-Pr	D	79	4:96	(**4a**:**5a**)
11	Me	*i*-Pr	D	70	11:89	(**4e**:**5e**)
12	*t*-Bu	*i*-Pr	D	79	7:93	(**4f**:**5f**)

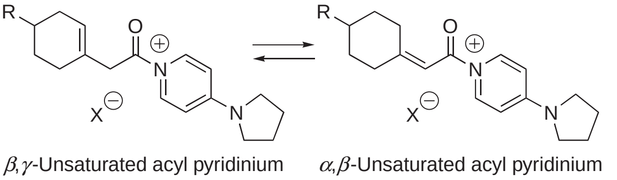
[a] A: rt, **1**–**3**/PPY/EDC•HCl (1:0.3:1.5), B: rt, **1**/PPY/DCC (1:0.3:1.5), C: rt, **1**/PPY/EDC (1:0.3:1.5), D: 0 °C, **1**–**3**/PPY/DCC (1:1.5:1.5). [b] Isolated yields. [c] Determined by ^{1}H NMR analysis of the crude esters. [d] Trimethylamine hydrochloride (1.5 mol equiv.) was added.

Table 2. Deconjugative amidation of 2-cyclohexylideneacetic acid **1**



Entry	R	Conditions[a]	Time/h	Yield/%[b]	**6**:**7**[c]
1	Bn	A	6	71	36:64 (**6a**:**7a**)
2	Ph	A	6	81	55:45 (**6b**:**7b**)
3	4-$NO_2C_6H_4$	A	21	45	100:0 (**6c**:**7c**)
4	Bn	B	6	18	0:100 (**6a**:**7a**)
5	Ph	B	24	10	0:100 (**6b**:**7b**)
6	4-$NO_2C_6H_4$	B	24	0[d]	—

[a]A: **1**/PPY/EDC•HCl (1:0.3:1.5), B: **1**/EDC•HCl (1:1.5). [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of the crude amides. [d]No reaction.



Scheme 1. Proposed migration of the double bond in acyl pyridinium intermediates.

The counter anion (X^-) seems to have a significant influence on the reactivity of these acyl pyridiniums. For reference's sake, it should be noted that Dai et al. reported that β,γ-unsaturated ester **4c** was thermodynamically more stable than α,β-unsaturated ester **5c**.[10] We are currently investigating the mechanism underlying and the extension of this intriguing deconjugative esterification.

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