doi:10.1246/cl.2012.189
Published on the web February 4, 2012

Deconjugative Esterification of 2-(4-Phenylcyclohexylidene)acetic Acid via Intramolecular Chirality Transfer

Shigeki Sano,* Takashi Ichikawa, Michiyasu Nakao, and Yoshimitsu Nagao
Graduate School of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770-8505

(Received December 3, 2011; CL-111160; E-mail: ssano@ph.tokushima-u.ac.jp)

Deconjugative esterification of optically active 2-(4-phenylcyclohexylidene)acetic acid (**1**) and 2-(4-*tert*-butylcyclohexylidene)acetic acid (**4**) with an axis of chirality afforded the corresponding β,γ-unsaturated esters **2** and **6**, each with a center of chirality. Additionally, a plausible reaction mechanism for the intramolecular chirality transfer is described.

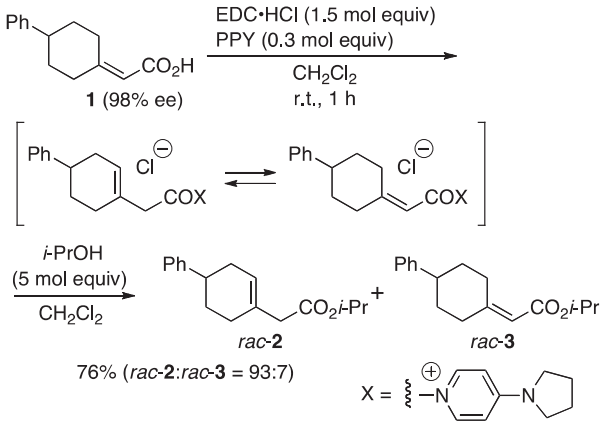
Our group has been interested in the stereoselective synthesis of carbon–carbon double bonds with an axis of chirality by Horner–Wadsworth–Emmons (HWE) reactions of 4-substituted-cyclohexanones and 2-substituted-1,3-dioxan-5-ones.[1] Recently, we reported the deconjugative esterification and amidation of 2-cyclohexylideneacetic acids.[2] In connection with the deconjugative esterification reaction, we investigated the stereocontrolled conversion of optically active 2-cyclohexylideneacetic acids with axis-to-center chirality transfer.[3]

At the outset, we examine the deconjugative esterification of optically active 2-(4-phenylcyclohexylidene)acetic acid (**1**) through β,γ-unsaturated acyl pyridinium intermediate as depicted in Scheme 1.[2a] Treatment of carboxylic acid **1** (98% ee)[4] with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) and 4-(pyrrolidin-1-yl)pyridine (PPY) in CH_2Cl_2 followed by the addition of excess amounts of *i*-PrOH led to *rac*-β,γ-unsaturated ester **2** and *rac*-α,β-unsaturated ester **3** with a **2**:**3** ratio of 93:7, and in 76% yield. Racemization of both esters **2** and **3** was also observed in a similar reaction with *N*,*N*-dimethyl-4-aminopyridine (DMAP) instead of PPY. Needless to say, it was anticipated that the equilibrium between acyl pyridinium intermediates, β,γ-unsaturated acylpyridinium and α,β-unsaturated acylpyridinium, caused the racemization of both esters **2** and **3**.[2a]

On the other hand, we investigated the deconjugative esterification of α,β-unsaturated carboxylic acid **1** through α,β-unsaturated ketene intermediate and found it to work well (Table 1).[2b] The esterification of **1** (98% ee) with *i*-PrOH in the presence of 1,3-dicyclohexylcarbodiimide (DCC), Me_3N·HCl, and Me_2NEt in CH_2Cl_2 gave β,γ-unsaturated ester **2** in 87% ee with a **2**:**3** ratio of 97:3, and in 79% yield (Table 1, Entry 2). Further, the efficacy of axis-to-center chirality transfer in the esterification of **1** (98% ee) was somewhat improved when 1,3-diisopropylcarbodiimide (DIC) was employed instead of DCC. In this reaction, β,γ-unsaturated ester **2** was obtained in 90% ee with a **2**:**3** ratio of 96:4 (74% yield) (Table 1, Entry 3).[5] In addition, no racemization of isolated product **2** (90% ee) was observed under the reaction conditions C in the absence of carboxylic acid **1**.[6]

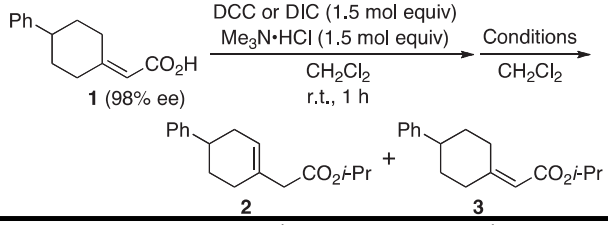
Based on these results, we further examined the deconjugative esterification of α,β-unsaturated carboxylic acid **1** through α,β-unsaturated ketene intermediate under microwave irradiation according to the previously optimized procedure.[2b] However, enantiomeric excesses of the resulting β,γ-unsaturated ester **2** by the reaction with DCC or DIC were moderate (Table 1, Entries 4 and 5). A lower reaction temperature was found to lead to an increase in enantiomeric excess values of **2** to some degree, but the yield was considerably decreased (Table 1, Entry 6).

The ee values of **2** and **3** were determined by HPLC analysis on a chiral stationary phase (CSP). Unfortunately, the absolute configurations of **1**, **2**, and **3** were not determined. Even so, the absolute configuration of 2-(4-*tert*-butylcyclohexylidene)acetic



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

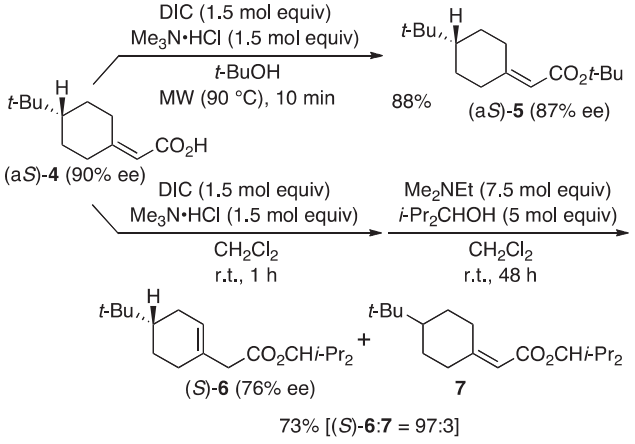
Table 1. Deconjugative esterification of α,β-unsaturated carboxylic acids **1**



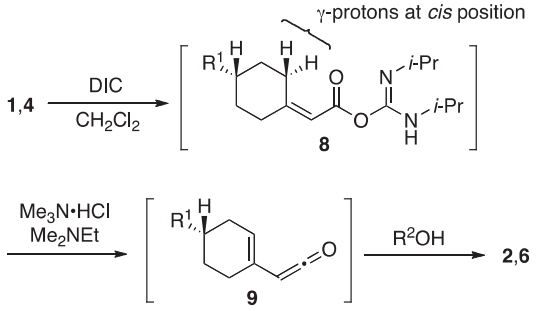
Entry	Conditions[a]	Yield/%[b]	**2**:**3**[c]	Ee/% of **2**[d]	Ee/% of **3**[d]
1	A	71	90:10	90	n.d.
2	B	79	97:3	87	n.d.
3	C	74	96:4	90	98
4	D	79	98:2	67	n.d.
5	E	81	97:3	65	n.d.
6	F	44	97:3	82	n.d.

[a]A: DCC, rt, 48 h, **1**/Et_3N/*i*-PrOH (1:7.5:5), B: DCC, rt, 48 h, **1**/Me_2NEt/*i*-PrOH (1:7.5:5), C: DIC, rt, 48 h, **1**/Me_2NEt/*i*-PrOH (1:7.5:5), D: DCC, MW (90 °C), 10 min, **1**/Me_2NEt/*i*-PrOH (1:3:1.5), E: DIC, MW (90 °C), 10 min, **1**/Me_2NEt/*i*-PrOH (1:3:1.5), F: DIC, MW (50 °C), 30 min, **1**/Me_2NEt/*i*-PrOH (1:3:1.5). [b]Isolated yields. [c]Determined by ^{1}H NMR (400 or 500 MHz, benzene-d_6) analysis of the crude esters. [d]Determined by HPLC analysis (CHIRALCEL OD-H, *n*-hexane/2-propaol).

© 2012 The Chemical Society of Japan



Scheme 2. Deconjugative esterification of 2-cyclohexylideneacetic acid (a*S*)-**4**.



Scheme 3. Deconjugative esterification of 2-cyclohexylideneacetic acids **1** and **4**.

acid (**4**) (90% ee)[7] was determined to be a*S* by chemical conversion to the known compound **5** [87% ee, $[\alpha]_D^{19}$ +56.4 (*c* 1.00, EtOH), lit[3b] (a*S*)-**5** (23% ee), $[\alpha]_D^{25}$ +14.5 (*c* 0.98, EtOH)] and by comparison of the specific rotation with the value in the literature as shown in Scheme 2. Then, deconjugative esterification of α,β-unsaturated carboxylic acid (a*S*)-**4** (90% ee) afforded β,γ-unsaturated ester (*S*)-**6** (76% ee) via intramolecular chirality transfer.[8] The absolute configuration of **6** [76% ee, $[\alpha]_D^{18}$ −49.0 (*c* 1.00, $CHCl_3$), lit[3b] (*R*)-**6** (46% ee), $[\alpha]_D^{25}$ +26.4 (*c* 1.06, $CHCl_3$)] was similarly determined to be *S* by comparing the specific rotation with the literature value. The ee value of **7** was not determined.

These results show that the reaction outcome may be rationalized by regioselective deprotonation of one of the γ-protons at the *cis* position relative to the carbonyl group of the *O*-acyl urea **8** for axis-to-center chirality transfer to lead to the chiral α,β-unsaturated ketene **9** (Scheme 3). The actual mechanism underlying this deconjugative esterification remains obscure, but the reaction mechanism underlying the deconjugative esterification in the presence of EDC•HCl and PPY (Scheme 1) should be different from those in the presence of DIC, Me_3N•HCl, and Me_2NEt (Table 1 and Scheme 2). The in situ formation of α,β-unsaturated ketene intermediate is plausible in the latter reaction.[9] By comparison with the latter reaction, deconjugative esterification of **1** (98% ee) and (a*S*)-**4** (82% ee) utilizing an ordinary ketene synthesis[10] from the corresponding acid chlorides and Et_3N exhibited moderate levels of chirality transfer.[11] The enantiomeric excess of the resultant β,γ-unsaturated esters **2** and **6** were 66% ee and 64% ee, respectively.

Despite our present lack of success in deconjugative esterification with a complete transfer of chirality, we believe that the procedure provides a novel methodology in asymmetric synthesis associated with asymmetric HWE reactions. Our efforts to improve the efficacy of the axis-to-center chirality transfer of 2-cyclohexylideneacetic acids are continuing, and the results will be reported elsewhere.

This work was supported in part by a Grant for the Regional Innovation Cluster Program (Global Type) promoted by MEXT.

References and Notes

1 S. Sano, K. Yokoyama, R. Teranishi, M. Shiro, Y. Nagao, *Tetrahedron Lett.* **2002**, *43*, 281; S. Sano, R. Teranishi, F. Nakano, K. In, H. Takeshige, T. Ishii, M. Shiro, Y. Nagao, *Heterocycles* **2003**, *59*, 793; S. Sano, S. Abe, T. Azetsu, M. Nakao, M. Shiro, Y. Nagao, *Lett. Org. Chem.* **2006**, *3*, 798.

2 a) S. Sano, E. Harada, T. Azetsu, T. Ichikawa, M. Nakao, Y. Nagao, *Chem. Lett.* **2006**, *35*, 1286. b) S. Sano, T. Ichikawa, M. Nakao, Y. Nagao, *Chem. Lett.* **2012**, *41*, 68.

3 For examples of axis-to-center chirality transfer of α,β-unsaturated carbonyl compounds by deconjugative reaction, see: a) L. Duhamel, A. Ravard, J.-C. Plaquevent, *Tetrahedron: Asymmetry* **1990**, *1*, 347. b) M. Iguchi, K. Tomioka, *Org. Lett.* **2002**, *4*, 4329.

4 Chiral α,β-unsaturated carboxylic acid **1** (98% ee) was obtained by enzymatic hydrolysis of ethyl ester of *rac*-**1** utilizing CAL-A (Roche) or Novozyme 735 (Novozymes) in 35% and 37% yield, respectively. The enantiomeric excess of resolution product **1** was determined by HPLC analysis (CHIRALCEL OD-H, *n*-hexane/2-propanol = 19/1) after methylation with (trimethylsilyl)diazomethane ($TMSCHN_2$).

5 The typical procedure was as follows. To a solution of 2-(4-phenylcyclohexylidene)acetic acid (**1**) (98% ee, 51 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (2.4 mL) were added DIC (46 µL, 0.35 mmol) and Me_3N•HCl (34 mg, 0.35 mmol) at room temperature. The mixture was stirred at room temperature for 1 h, and then Me_2NEt (190 µL, 1.77 mmol) and *i*-PrOH (90 µL, 1.18 mmol) were added to the solution. After being stirred at room temperature for 48 h under argon, the reaction mixture was treated with H_2O (10 mL) and then extracted with $CHCl_3$ (30 mL × 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue (**2**:**3** = 96:4) was purified by silica gel (Kanto Chemical 60N) column chromatography [*n*-hexane–AcOEt (40:1)] to afford the mixture of **2** (90% ee) and **3** (98% ee) as a colorless oil (46 mg, 74% yield). The ee values of **2** and **3** were determined by HPLC analysis [column: CHIRALCEL OD-H, eluent: *n*-hexane/2-propanol = 500/1, flow rate: 1.0 mL min^{-1}, detection: 254 nm, t_R of **2** (major): 10.93 min, **2** (minor): 13.69 min, **3** (major): 11.56 min, **3** (minor): 16.08 min].

6 No racemization of isolated **2** (89% ee) was observed under the reaction conditions [**2**/*N*,*N*′-dicyclohexylurea/Me_2NEt/*i*-PrOH (1:1.5:7.5:5), rt, 12 h]. Isomerization of *rac*-**3** to *rac*-**2** was not observed under the similar reaction conditions [**3**/*N*,*N*′-dicyclohexylurea/Me_2NEt/*i*-PrOH (1:1.5:7.5:5), rt, 12 h].

7 Optical resolutions of *rac*-**4** by (−)-cinchonidine from $CHCl_3$/*n*-hexane gave (a*S*)-**4** (90% ee).

8 The ee value of (*S*)-**6** (76% ee) was determined by HPLC analysis [column: CHIRALCEL OD-H, eluent: *n*-hexane/2-propanol = 4000/1, flow rate: 0.3 mL min^{-1}, detection: 220 nm, t_R of (*R*)-**6**: 22.30 min, (*S*)-**6**: 24.40 min].

9 A. Maquestiau, P. Pauwels, R. Flammang, P. Lorenčak, C. Wentrup, *Org. Mass Spectrom.* **1986**, *21*, 259; V. Theodorou, M. Gogou, M. Philippidou, V. Ragoussis, G. Paraskevopoulos, K. Skobridis, *Tetrahedron* **2011**, *67*, 5630.

10 G. B. Payne, *J. Org. Chem.* **1966**, *31*, 718; G. Cardillo, S. Fabbroni, L. Gentilucci, R. Perciaccante, A. Tolomelli, *Tetrahedron: Asymmetry* **2004**, *15*, 593; A. R. Lingham, H. M. Hügel, T. J. Rook, *Aust. J. Chem.* **2006**, *59*, 340.

11 Acid chlorides were prepared by the reaction of **1** (98% ee) and (a*S*)-**4** (82% ee) with oxalyl chloride (2 mol equiv) in CH_2Cl_2, and were used for further esterification in the presence of *i*-PrOH (5 mol equiv) without isolation from the reaction medium.

 © 2012 The Chemical Society of Japan