

Stereo-Selective Synthesis of 5-Norbornene-2-*exo*-carboxylic Acid—Rapid Isomerization and Kinetically Selective Hydrolysis

Miki Kanao, Atsushi Otake, Kousuke Tsuchiya, Kenji Ogino

Graduate School of Bio-Applications and Systems Engineering,
Tokyo University of Agriculture and Technology, Tokyo, Japan
Email: kogino@cc.tuat.ac.jp

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ABSTRACT

Simple and efficient stereo-selective synthesis of *exo*-5-norbornene-2-carboxylic acid (NBCA) is reported. Preliminary studies on base promoted isomerization of methyl 5-norbornene-2-carboxylate (MNBC) revealed that rapid isomerization was accomplished with sodium *tert*-butoxide (tBuONa), and the *exo*-content at the equilibrium was ca. 60%. The hydrolyses of *endo*-rich MNBC (*endo/exo* = 80/20) under various conditions were carried out. The *exo* selectivity for resulting NBCA was improved when the hydrolysis was conducted with equimolar water at room temperature in the presence of the stronger base (tBuONa) (*endo/exo*: 18/82). Whereas the use of excess amount of water led to rapid and non-selective hydrolysis affording high *endo* content of the product. The plausible reaction mechanism involving rapid equilibrium of thermodynamic isomerization and kinetically preferred hydrolysis of *exo* ester is proposed.

Keywords: Stereo-Selective Synthesis; 2-Substituted Norbornene; Isomerization; Kinetically Selective Hydrolysis

1. Introduction

5-Norbornene-2-carboxylic acid and its derivatives are important as intermediates of pharmaceutically and biologically active compounds and monomers for advanced polymeric materials. 2-Substituted norbornene compounds can be conventionally obtained by Diels-Alder cycloaddition between cyclopentadiene and acrylic compounds. It is well-known that Diels-Alder cycloaddition is *endo*-selective due to secondary orbital overlap, and the selectivity is enhanced by Lewis acid [1,2]. Polynorbornenes, which can be synthesized by vinyl polymerization or ring-opening metathesis polymerization (ROMP) of norbornene derivatives, show high thermal stability and transparency, and are useful for optical applications such as optical fibers, disk, lens and displays [3,4]. Norbornene derivatives are also useful as monomers or intermediates for photoresist materials [5,6]. *Exo*-isomer of norbornene carboxylic ester shows higher reactivity in living ROMP than *endo*-isomer [7]. In the case of photoresist monomer synthesis, *endo*-isomer provides undesired lactone by intramolecular cycloaddition to result in a low yield of desired photoresist monomer [8]. As can be seen in the two examples, *exo*-selective synthesis of norbornene carboxylic acid derivatives is of importance from the practical viewpoint.

Some of *exo*-selective syntheses of norbornene derivatives have been reported. Gouverneur *et al.* reported asymmetric Diels-Alder reaction by using antibody catalyst [9]. Fraile reported asymmetric Diels-Alder reaction of furan with chiral acrylate [10]. Avenoza and Kawamura reported asymmetric Diels-Alder reaction of cyclopentadiene and chiral dienophile [11,12]. Because of high cost of these reactions, practically pure *exo*-isomer is obtained by removing of *endo*-isomer through lactonization [13, 14]. Previously we reported *exo*-selective synthesis of 5-norbornene-2-carboxylic acid from *endo*-rich carboxylate in order to investigate the effect of *endo/exo* ratio on performance of photoresist prepared from *tert*-butyl 5-norbornene-2-carboxylate [15]. High *exo*-content and yield of the product cannot be explained only by *exo*-selective hydrolysis as reported by of Niwayama and Hiraga [16]. As the plausible mechanism, we proposed that hydrolysis should be carried out accompanying with *endo/exo* isomerization.

In this paper, various experimental parameters including reaction solvent, temperature, type of base, and the amount of water were optimized in order to afford simple and efficient synthetic method for *exo*-norbornene carboxylic acid, and confirm our hypothesis about *exo*-selective hydrolysis.

2. Experiment

2.1. Materials

5-Norbornene-2-carboxylate (MNBC) and *tert*-butyl 5-norbornene-2-carboxylate (tBNBC) were synthesized via conventional Diels-Alder cycloaddition reaction according to the previous work [15]. The ratio of *endo/exo* was determined as 80/20 by ¹H-NMR and HPLC. Sulfuric acid was obtained from Aldrich. Tetrahydrofuran (THF) was purchased from Wako Pure Chemical Industries, Ltd., and dehydrated by distillation under nitrogen with sodium/benzophenone. All other materials were purchased from Wako Pure Chemical Industries, Ltd. and used without any further purification unless otherwise mentioned.

2.2. General Procedure for Synthesis of *exo*-Rich 5-Norbornene-2-carboxylic acid (NBCA)

THF solution of base (1 mol/L) was charged into a two-necked flask equipped with a dropping funnel under nitrogen atmosphere. MNBC (*exo*; 20%, 0.4 mol/L) was added into the flask and stirred at room temperature for 3 h. One or ten equivalents of deionized water diluted with THF was added into the reaction mixture dropwise, and the reaction was continued for 24 h at predetermined temperature. In order to complete the hydrolysis, excess amount of deionized water was added. The reaction mixture was stirred for 1 h at room temperature and was neutralized with acetic acid until pH was adjusted to 7.5. The excess solvent was removed under reduced pressure. After the addition of 35% HCl until pH was adjusted to 2.0, the reaction mixture was extracted with toluene three times. Toluene was removed under reduced pressure, and the product was dried in vacuo over night to give NBCA.

2.3. Synthesis of *exo*-Rich Methyl 5-Norbornene-2-carboxylate (MNBC)

5-Norbornene-2-carboxylic acid (9.40 g, 68 mmol, *exo*; 72), methanol (8.30 mL, 0.20 mol), dichloromethane (20 mL) and 98%-sulfuric acid (0.28 mL, 5.0 mmol) were added into 100 mL-three-necked flask. The mixture was heated and refluxed for 17 h, and cooled to room temperature. After addition of deionized water, the reaction mixture was extracted with dichloromethane and the extract was washed with sat. NaHCO_{3(aq)}. The solvent was removed under reduced pressure to give methyl 5-norbornene 2-carboxylate (9.63 g, 93%, *exo*; 75%).

2.4. Characterization

¹H-NMR spectra were obtained on a JEOL ECX-500 instrument at 500 MHz. The ratio of *endo*- and *exo*-isomers of MNBC, NBCA, and tBNBC were determined from

peak intensities of each isomer by ¹H-NMR in chloroform-*d* at 25°C. The ratio of MNBC and NBCA were also determined by HPLC; JASCO C-Net II/ADC system, UV-detector; JASCO UV-2075 (224 nm), column; SC PEGASIL ODS-2352 (4.6 mm i.d., 18 cm), eluent; distilled water/methanol = 4/6 (1 mL/min), pH was adjusted to 3 by phosphate buffer, retention time; *exo*-isomer 7.4 min, *endo*-isomer 8.6 min. The ratio determined by HPLC was calibrated by NMR.

3. Results and Discussion

Figure 1 shows ¹H-NMR spectrum of MNBC synthesized via a conventional Diels-Alder cycloaddition reaction as a starting material. The mole ratio of *endo/exo* was determined as 80/20. In order to obtain 5-norbornene-2-*exo*-carboxylic acid (*exo*-NBCA), isomerization from *endo*-isomer to *exo*-isomer is required. As MNBC has an active proton at α -position of carbonyl group, the corresponding carbanion can be generated by elimination of the proton in basic conditions. In general, carbanion has *sp*³-type trigonal pyramid structure, and low activation barrier for the inversion of this geometry. By utilizing the continuous inversion, the mixture comprising mainly *endo*-isomer of MNBC can be isomerized to corresponding *endo/exo* mixture of which ratio is ruled by thermodynamic equilibrium under basic conditions.

Figure 2(a) shows temperature dependence of isomerization of *endo*-rich MNBC in the presence of sodium methoxide (CH₃ONa). At room temperature, the rate of isomerization was slow, and the reaction did not reach its equilibrium (the *exo*-content increased to about 35% from 20%). When the solvent was changed to THF from methanol, the kinetics of isomerization and thermodynamic equilibrium were not changed. The kinetics of isomerization and *exo*-ratio was not dependent on the solvent. At elevated temperatures (40°C and 60°C), the *exo* content approached to 50%, and the equilibrium was almost established within 2 h. Maximum *exo* content remained at 50% even heated at 67°C (not shown). As shown in **Figure 2(b)**, a strong base (tBuONa) effectively promoted the isomerization to reach thermodynamic equilibrium (*exo* content ca. 60%) rapidly even at room temperature in 10min. When *exo*-rich MNBC (*exo*-ratio; 75%) was used as a starting materials, the ratio of *exo*-isomer in the equilibrium was also the same as that obtained with *endo*-rich MNBC. In the case of norbornene dicarboxylic acid anhydride, *exo*-isomer is known to be thermodynamically more stable than *endo* isomer [16]. These results suggest that a slight difference of thermodynamic stability between *endo*- and *exo*-isomers of norbornene monocarboxylate carbanion exist, but it is negligible above 40°C.

The kinetics difference of hydrolysis of *endo*- and *exo*-

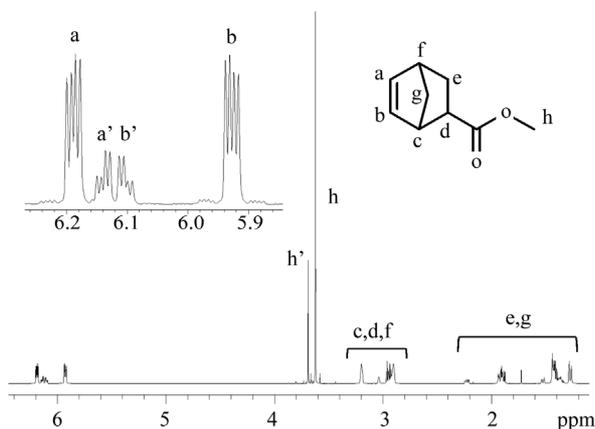
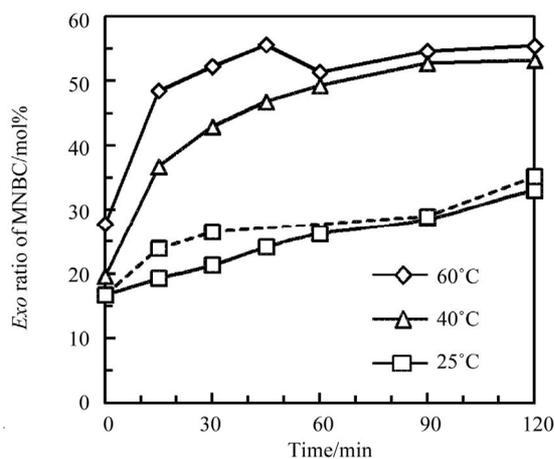
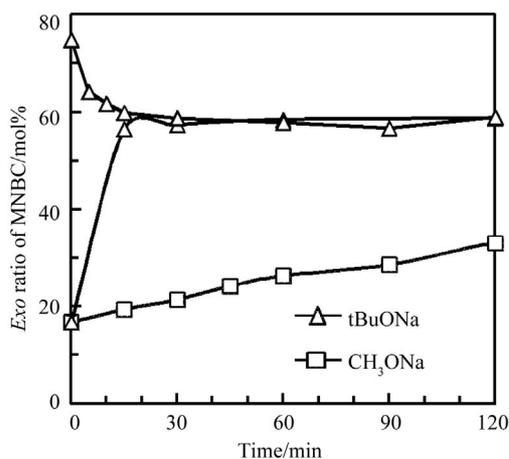


Figure 1. $^1\text{H-NMR}$ spectrum of *endo*-rich mixture of methyl 5-norbornene-2-carboxylate measured at 500 MHz in CDCl_3 (*endo/exo* = 82/18).



(a)



(b)

Figure 2. *Endo-exo* isomerization of MNBC (a) Temperature dependence using CH_3ONa in methanol (solid line) or THF (broken line) ($\text{MNBC}/\text{CH}_3\text{ONa} = 1/2.2$, $[\text{MNBC}] = 0.45 \text{ M}$); (b) Base dependence in THF at 25°C ($\text{MNBC}/\text{base} = 1/2.2$, $[\text{MNBC}] = 0.45 \text{ M}$).

MNBC can be utilized to obtain *exo*-rich mixture of NBCA. As suggested by Niwayama [16], the rate of hydrolysis of *exo*-isomer is expected to be faster than that of *endo*-isomer due to the steric hindrance of norbornene ring.

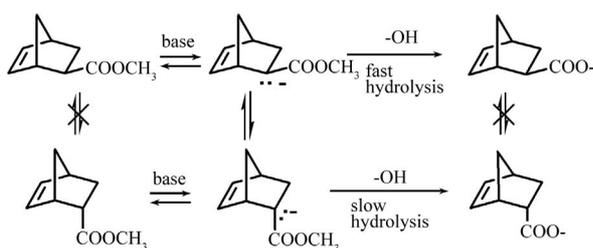
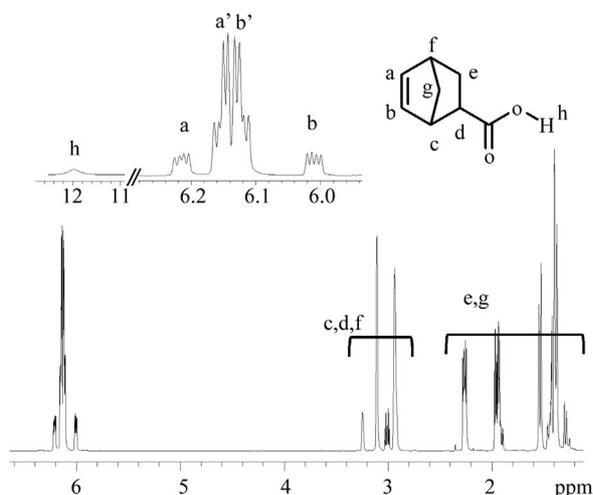
In order to obtain *exo*-rich mixture of NBCA in a high yield, it is considered that kinetically *exo*-selective hydrolysis should occur accompanied by the rapid isomerization from *endo*- to *exo*-isomer. As described in the previous section, part of esters is considered to exist as the corresponding carbanions under basic conditions allowing mutual isomerization. However, once the hydrolysis proceeds, resulting carboxylate anion does not generate carbanion because of high energy level of resulting dianion, which means that isomerization carboxylate anion is suppressed, while ester is isomerized through continuous inversion via the carbanion. Therefore, kinetically *exo*-selective hydrolysis accompanied by a rapid isomerization of ester enables to generate *exo*-carboxylic acid in a high yield as illustrated in **Scheme 1**.

In this study typical hydrolysis experiments were carried out by adding water into the solution of MNBC and CH_3ONa or tBuONa , or potassium *tert*-butoxide (tBuOK). **Table 1** lists experimental conditions and results. In all experiments, *exo*-rich NBCA was obtained compared with starting ester (*exo*-ratio; 20%) in high conversions, which supports the mechanism described in **Scheme 1**. Run 1 was carried out under almost the same conditions as a previous report [8,15]. By changing the solvent from methanol to anhydrous THF, *exo* selectivity increased slightly and the conversion was improved. In Run 3, excess amount of water was rapidly added into the reaction mixture. As a result, low *exo*-ratio was observed since nonselective hydrolysis occurred due to high concentration of water. Lowering temperature is expected to increase *exo*-ratio by the improvement of the selectivity of hydrolysis, but resulted in lower *exo*-ratio at room temperature (Run 4) probably due to slow isomerization as shown in **Figure 2(a)**. The rate of isomerization was accelerated by stronger base, tBuONa as shown in **Figure 2(b)**. By using tBuONa as a base, *exo*-ratio increased significantly (Run 6, **Figure 3** shows $^1\text{H-NMR}$ spectrum). When the reaction was carried out at higher temperature (Run 5), *exo*-ratio slightly decreased because the selectivity decreased because of the high hydrolysis rate. Decreasing temperature to 5°C provided slightly lower *exo*-content than at room temperature (Run 7). It may be due to slow isomerization similar to the case of Run 3. In the case using tBuOK as a base (Run 8), *exo*-ratio was almost the same as that with tBuONa (Run 6). Acidic hydrolysis led to low *exo*-content with relatively low conversion, suggesting that *endo/exo* isomerization occurs under only basic conditions (Run 9). Hydrolyses of another ester, *tert*-butyl 5-norbornene-2-carboxylate (tBNBC)

Table 1. Conditions and results of hydrolysis.

| Run | NB ester | Base | Temperature | Reaction time | Solvent | Conversion ^a | Exo-ratio of NBCA ^a |
|----------------|----------|----------------------------------|-------------|---------------|----------|-------------------------|--------------------------------|
| | | | (°C) | (h) | | (mol%) | (mol%) |
| 1 ^b | MNBC | CH ₃ ONa ^c | 60 | 24 | methanol | 82 | 62 |
| 2 | MNBC | CH ₃ ONa | 60 | 17 | THF | >99 | 70 |
| 3 ^d | MNBC | CH ₃ ONa | 25 | 17 | THF | 74 | 33 |
| 4 | MNBC | CH ₃ ONa | 25 | 17 | THF | >99 | 61 |
| 5 | MNBC | tBuONa | 60 | 17 | THF | >99 | 74 |
| 6 | MNBC | tBuONa | 25 | 17 | THF | 95 | 82 |
| 7 | MNBC | tBuONa | 5 | 21 | THF | >99 | 72 |
| 8 | MNBC | tBuOK | 25 | 17 | THF | >99 | 80 |
| 9 ^e | MNBC | - | 67 | 18 | THF | 77 | 50 |
| 10 | tBNBC | tBuONa | 60 | 17 | THF | <5 | 85 |
| 11 | tBNBC | tBuONa | 25 | 17 | THF | <5 | 81 |

^aConversion and the ratio of isomers were determined by HPLC calibrated by ¹H-NMR; ^bReference data from previous work [8,15]; ^c28 wt% Sodium methoxide methanol solution was used; ^dExcess amount of water (10 eq vs MNBC) was added; ^eAcidic hydrolysis using conc. H₂SO₄.

**Scheme 1. Reaction mechanism of stereo-selective synthesis.****Figure 3. ¹H-NMR spectrum of *exo*-rich mixture of 5-norbornene-2-carboxylic acid measured at 500 MHz in CDCl₃ (*endo:exo* = 18/82, run 6 in Table 1).**

were also investigated under similar conditions. As expected, high *exo*-content of products were obtained with low conversions due to the steric hindrance (Runs 10, 11). It is considered that high selectivity in hydrolysis is still valid.

Presented results indicate that hydrolysis with equimolar water in the presence of a strong base at moderate temperature provides high stereo-selectivity in the conversion of MNBC to NBCA. In order to obtain high *exo*-ratio of NBCA, both rapid isomerization and slow hydrolysis are required.

4. Conclusion

We investigated the relationship between the *exo*-selectivity and conversion in hydrolysis reaction of MNBC, and the experimental conditions including basicity, solvent, and temperature. High selectivity with high conversion was accomplished by the slow hydrolysis with equimolar water in the presence of a strong base (tBuONa) at room temperature. Based on the results, a plausible mechanism for high selectivity is proposed which involves the rapid isomerization of a reactant during slow and selective hydrolysis, and relatively slow isomerization of resulting carboxylate anions. In conclusion, *exo*-5-norbornene carboxylic acid was synthesized by simple and efficient procedure, and the proposed method provides isomerically rich compound without chiral materials, catalysts, strict reaction conditions.

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