Enantio-Differentiating Hydrogenation of Methyl 2-Furoylacetate and Its Analogs over Tartaric Acid-Modified Raney Nickel

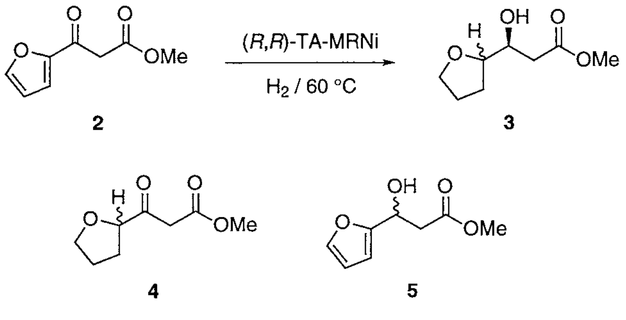
Satoshi Nakagawa, Noriko Haruna, Delicia E. Acosta,† Tadateru Endo, Takashi Sugimura,* and Akira Tai
Faculty of Science, Himeji Institute of Technology, Kohto Kamigori, Ako-gun, Hyogo 678-1297
†*JAICA Research Fellow from INIQUI, National University of Salta, Buenos Airess, 177 440 Salta, Argentina*

(Received July 5, 1999; CL-990593)

Hydrogenation of methyl 2-furoylacetate over TA-MRNi reduced the three unsaturated bonds to give methyl tetrahydro-2-furoylacetate, the enantiomeric excess (ee) of which at the 3-position was 77%, whereas the 4-position was racemic. Under the same conditions, the substrate of 4-methoxycarbonyl analogue was resulted in hydrogenation of only the ketone moiety to give the corresponding chiral *sec*-alcohol having a furan ring in 69% ee.

Tartaric acid-modified Raney nickel (TA-MRNi) is a heterogeneous catalyst for the enantio-differentiating hydrogenation of ketones that produces optically active *sec*-alcohols.[1] After the long term investigation to improve the enantio-differentiating ability of TA-MRNi, the enantiomeric excess (ee) of the produced alcohol from methyl acetoacetate attained 86%.[2] Recently, it was found that the product ee from the β-ketoester depends on the structure of the substrate and the hydrogenation temperature,[3] and by these optimizations, an almost perfect enantio-differentiation resulting in over 98% ee has been achieved.[4] However, the reported β-ketoesters used as substrates for the TA-MRNi system were limited in alkyl substituted β-ketoesters or ω-functionalized-β-ketoesters. If a β-ketoester having an additional functional group near the reaction site could be hydrogenated with good enantio-differentiation, the versatility of the TA-MRNi system is increased, and a more valuable optically active alcohol can be obtained. In this communication, we report that the hydrogenation of the β-ketoesters, **2** and its analogs **6** and **8**, containing a furan moiety besides the reaction site performed under moderately high enantioface differentiation of the ketone moiety.

From the proposed model for the enantio-differentiation of β-ketoesters over TA-MRNi (stereochemical model), two-hydrogen bonding between the two hydroxyl groups in the tartaric acid adsorbed on the nickel and the two carbonyl groups in the substrate fix the enantioface of the ketone moiety to be hydrogenated,[1] and the bulkiness at the γ-position of the substrate enhances the participation of the hydrogen bonding.[3] Thus, the functional group containing an oxygen or nitrogen atom near the reaction site is expected to disturb the desired hydrogen bonding between the chiral modifier and the β-ketoester moiety in the substrate, and as a result, differentiation of the enantioface at the ketone moiety will become weaker. The oxygen substitution effect on the β-ketoester was tested using methyl 4-methoxy-3-oxobutanoate (**1**) as a simple model substrate having an ether oxygen at the γ-position. The hydrogenation of **1** over TA-MRNi by the reported method[2] resulted in 51% ee determined by GLC analysis (CP-Chiralsil DEX-CB). To reduce the oxygen substitution effect, we expected that the substrate **2** also having an ether oxygen at the γ-position could be hydrogenate with good enantio-differentiation, since the oxygen atom on the furan ring has a poor ability to form hydrogen bonding (dipole moment of tetrahydrofuran, 1.70 Debye; furan, 0.66 Debye). The substrate **2** was synthesized from 2-acetylfuran and dimethylcarbonate and purified by fractional distillation (77% yield). When **2** was hydrogenated at 60 °C (H_2, 10^7 Pa) over TA-MRNi for 68 h, three unsaturated bonds in **2** were reduced, producing a mixture of four stereoisomers of **3**. The isomer ratio was determined by capillary GLC analysis (CP-Chiralsil DEX-CB, 25 m, 120 °C) after acetylation of the mixture to give four separated peaks at 15.5, 15.8, 18.7, and 19.0 min in a ratio of 7/45/4/44. The relative stereochemistry of the two diastereomers was assigned by stereoselectivity of the hydride reduction of **4**. That is, **4** prepared from (±)-tetrahydro-2-furoic acid and Meldrum's acid was treated with $NaBH_4$ in methanol to give a mixture of **3** in a ratio of 32/32/18/18 (the same order as above), where the major diastereomers in this reaction could be assigned to be *threo*.[5] The absolute stereochemistry at the 3-position was determined to be (3*S*) rich for both diastereomers by the ^1H NMR analysis of the (*R*)-MTPA ester of the reaction mixture.[6] The assigned stereochemistries are indicated in Table 1, entry 1. The diastereomer ratio was *threo*/*erythro* = 52/48 and ee's were 73% for *threo* and 82% for *erythro*. The enantiomeric excess at the 3-positions was 77% and that at the 4-position was 2%.



Scheme 1.

The hydrogenation of **2** to **3** has two possible pathways: saturation of the C=O bond then the two units of the C=C on the furan ring or the reverse order. Thus, two intermediates, **4** and **5**, were expected. When the hydrogenation of **2** was interrupted before the completion of the hydrogen uptake, both **4** and **5** were detected along with **3**. The composition of **2**–**5** under the same conditions except for the shorter hydrogenation time was determined by the ^1H-NMR analysis, the results of which are indicated in Figure 1. Since the maximum contents of **5** reached 30% (at 6 h), the major reaction pathway during the hydrogenation of **2** was presumed to be through **5**.

The hydrogenations of racemic **4** and **5** were also performed

Table 1. Stereoisomers ratio of **3** of the hydrogenation mixture over TA-MRNi

Entry no.	Substrate	Reaction time	Isomers ratio of **3** (3*R*,4*R*)/(3*S*,4*S*)/(3*R*,4*S*)/(3*S*,4*R*)	Ratio of *threo*/*erythro*	Ee of *threo*	Ee of *erythro*	Ee at 3-position	Ee at 4-position
1	**2**	68 h	7.0 / 44.7 / 4.3 / 43.9	52/48	73	82	77	2
2	**4**	68 h	13.8 / 41.1 / 9.1 / 36.0	55/45	50	60	54	–
3	**5**	20 h	20.8 / 21.3 / 28.8 / 29.1	42/58	–	–	–	0

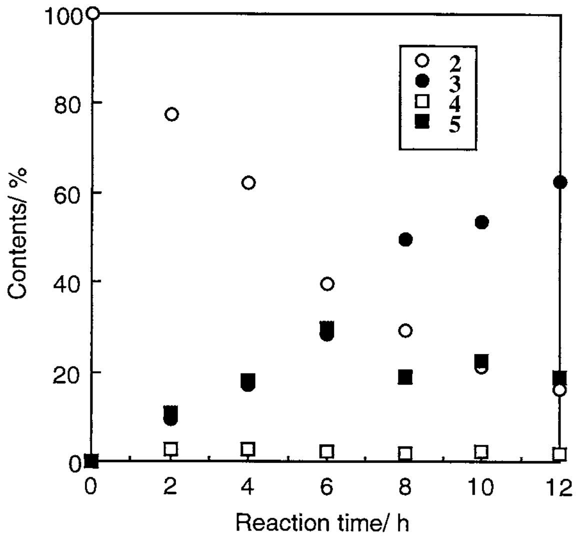
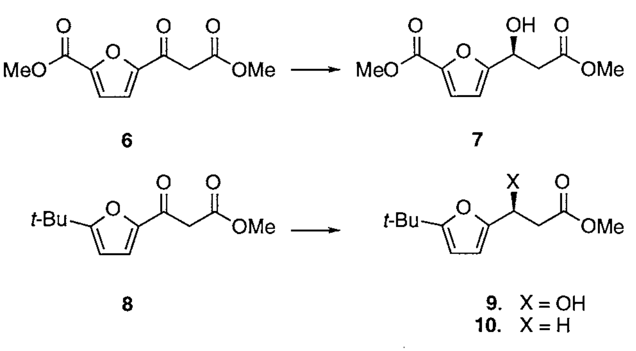


Figure 1. Composition of the substrate **2** and the products, **3**–**5**, as a function of the hydrogenation time.

using the TA-MRNi catalyst under the same conditions (Table 1, entries 2 and 3). The enantio-differentiation at the 3-position during the reaction of **4** was 54% of (*S*) excess, the same level of that of **1**. During the hydrogenation of **5**, the produced chirality at the 4-position was again racemic from both (3*R*)- and (3*S*)-**5**. Thus, although the enantio-differentiation of **2** was still not as high as that with a simple β-ketoester, the substrate design based on the stereochemical model, control of the hydrogen bonding ability of the substrate, was proved to be effective for functionalization of the substrate for the TA-MRNi system.

From a synthetic view point, a produced optically active *sec*-alcohol having a furan unit is more valuable since a furan unit can be converted to the varied functionalities. To interrupt the hydrogenation of a furan ring in the substrate and to obtain a furan-containing chiral alcohol, two substrates having a potent removable substituent group on the furan ring were designed. One is **6** having an extra ester group at the 4-position. From the results of the reaction of **2**, it was expected that the C=C bonds in a furan conjugated to a carbonyl group at the 2- or 4-position survive under the hydrogenation conditions. The other substrate **8** has a *tert*-butyl group at the 4-position as a steric fence, which is expected to reduce the reactivity of the C=C bonds.



Scheme 2.

The substrates of **6** and **8** were prepared through the similar procedure used for **2**. When **6** was hydrogenated under the same conditions for 24 h, the ketone moiety in **6** was reduced completely without any side-reactions to give the expected **7** in a quantitative yield.[7] From the GLC analysis, ee of **7** was determined to be 69%, which indicates a partial reduction of the enantio-differentiation in **2**. In the case of **8**, the C=C bonds were also retained under this conditions, but the over reduced product **10** was also produced. Ee of **9** was determined by the GLC analysis to be 79%.[8]

In the present study, we found that the TA-MRNi catalysis can perform enantio-differentiation during the hydrogenation of the β-ketoester containing an additional heteroatom besides the reaction site, when the ability of the hydrogen bonding with the extra heteroatom is properly reduced. The detailed study of the relation of the enantio-differentiation and the structure of the substrate is now in progress.

References and Notes

1 A. Tai and T. Harada, in "Tailored Metal Catalysis," ed by Y. Iwasawa, Reidel, Dordrecht (1986), pp. 265–324.

2 A. Tai, T. Kikukawa, T. Sugimura, Y. Inoue, S. Abe, T. Osawa, and T. Harada, *Bull. Chem. Soc. Jpn.*, **67**, 2473 (1994).

3 T. Sugimura, T. Osawa, S. Nakagawa, T. Harada, and A. Tai, in "Studies in Surface Science and Catalyst 101 (11th International Congress on Catalysis)," ed by J. W. Hightower, Elsevier, Amsterdam (1996), pp. 231–240.

4 S. Nakagawa, T. Sugimura, and A. Tai, *Chem. Lett.*, **1997**, 859.

5 Reduction of **3** with $NaBH_4$ in methanol afforded a mixture of **2** in a ratio of 32/32/18/18. The major diastereomer was assigned to be *threo*. M. Larcheveque and J. Lalande, *Bull. Soc. Chim. Fr.*, **1987**, 116. Reduction of the obtained mixture of **2** with $LiAlH_4$ and acetalization with 2-methoxypropene afforded a mixture of two diastereomers. A ^1H-NMR study of the isolated each isomer supported the above assignment.

6 Racemic **3** was prepared from tetrahydro-2-furoic acid and Meldrum's acid. Racemic **4** was prepared by the $NaBH_4$ reduction of **1**.

7 Optical rotation of isolated **7**: $[\alpha]_D^{20} = -30.8$ (c 0.5, $CHCl_3$)

8 The ratios of **10**/**9** in the repeated runs were in a range of 1–3. Kinetic resolution of **9** during the hydrogenation was not observed.