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# Isomerization of enol esters derived from 2-acyl-1,3-cyclohexanediones: mechanism and driving force

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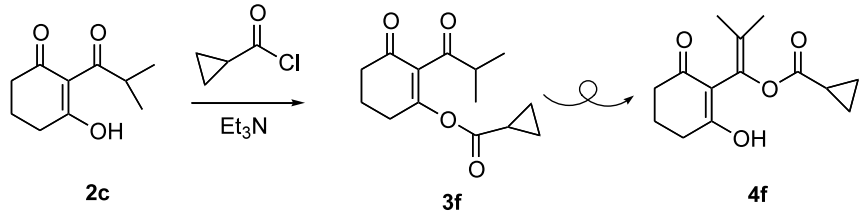
**Abstract**—A series of 2-acyl-1,3-cyclohexanediones were prepared and isomerization mechanisms of the corresponding enol esters were investigated. The driving force for this migration is likely that the intrinsic electrostatic repulsion between the 2-acyl oxygen atom and the two 1,3-diketone oxygens caused deformation of enol esters from planarity and resulted in their high susceptibility to enolization and subsequent isomerization. 

2-Acyl-1,3-cyclohexanediones and their derivatives have long been known for their extensive application as biologically active substances. For example, the two classes of commercially available herbicides sethoxydim[1] and sulcotrione,[2] which both contain a 2-acyl-1,3-cyclohexanedione moiety, are potent inhibitors of aceyl-CoA carboxylase (ACCase)[3] and 4-hydroxyphenylpyruvate dioxygenase (HPPD),[4] respectively. Recently, the triketone functionality in 2-acyl-1,3-cyclohexanediones has also been used as a primary amine protection group[5] and a linker in solid phase peptide synthesis.[6] In our continuing efforts to explore a new type of potent HPPD inhibitors to serve as an alternative treatment for the life-threatening tyrosinaemia type I disease,[7] we discovered an unexpected isomerization of enol esters derived from 2-acyl-1,3-cyclohexanediones. When 2-isobutyryl-1,3-cyclohexanedione **2c** was treated with cyclopropanecarbonyl chloride in the presence of triethylamine as a base in methylene chloride, the corresponding ester **3f** formed quantitatively. The resulting enol ester **3f** isomerized to compound **4f** at room temperature with or without solvent, as shown in Scheme 1. The structure of **4f** was unequivocally characterized by X-ray crystallographic analysis as depicted in Figure 1.[8] In this paper, we address the issues of the mechanism and driving force of this isomerization.

A series of 2-acyl-1,3-cyclohexanediones with a different side chain on the 2-acyl group were prepared to test the broadness of this migration as well as to explore the factors affecting the rate of the isomerization. The synthetic route to compounds **2a–e** is outlined in Scheme 2. The first event was *O*-acylation of 1,3-cyclohexanedione by appropriate acyl chloride to give enol ester **1**, which on treatment with cyanide ion and a base rearranged to the corresponding *C*-acyl isomers **2a–e**.[9] Compounds **2a–e** were then subjected to the migration by treating with an excess of acetyl chloride or cyclopropanecarbonyl chloride. The isomerization products were isolated and characterized as shown in Scheme 3.[10] The two ester groups on **5a–j** can be removed readily upon microwave irradiation (in montmorillonite K10, 800 W, 2–3 min) to recover quantitatively the starting




**2c** **3f** **4f**

**Scheme 1.**

*Keywords*: isomerization; mechanism; driving force.

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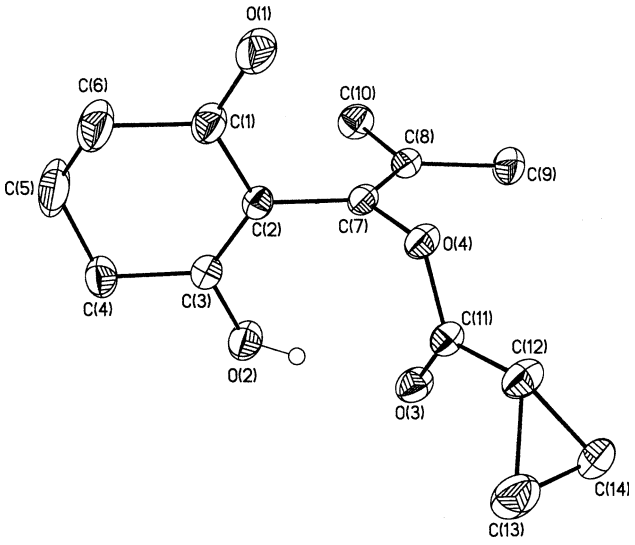
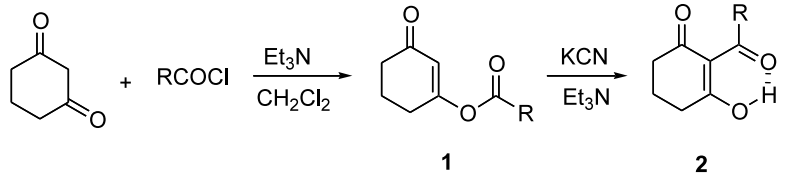
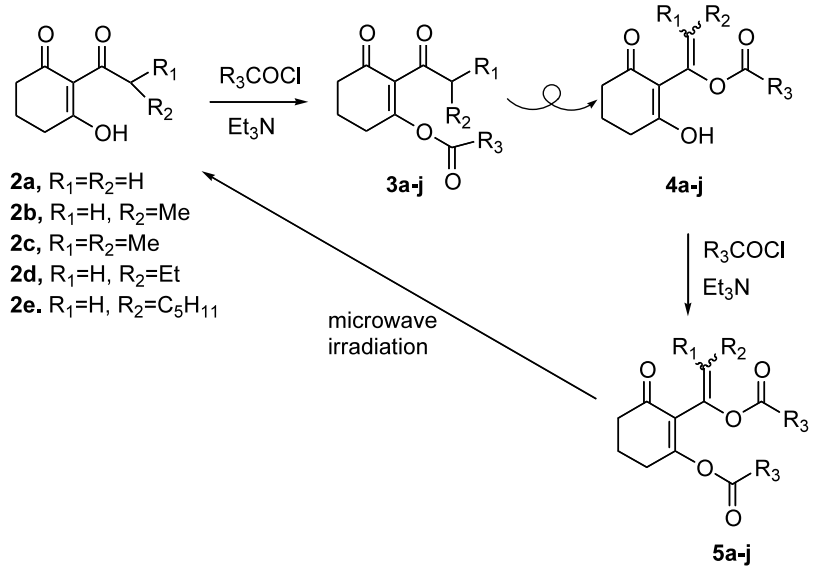



**Figure 1.** X-Ray structure of **4f**. ORTEP diagram showing the crystallographic atom-numbering scheme; small open circle represents a hydrogen atom.

materials **2a**–**e**. The isomerization yields and $E/Z$ ratios of possible geometrical isomers were examined and summarized in Table 1. According to Table 1, the yield for the isomerization reaction is governed by the bulkiness of both the side chains on 2-acyl group and the 3-ester functionality. A rapid and complete isomerization of 2-acyl-1,3-cyclohexanedione enol ester was observed when a relatively small 2-acyl group like acetyl or propionyl was used as the substrate. Moreover, 2-acyl-1,3-cyclohexanedione with a smaller 3-enol ester group rearrange faster than with a bulkier ester group. For example, compound **2** with those $R_3$ being a methyl group always gives a better isomerization yield than with $R_3$ being a cyclopropyl group. In addition, when a 2-cyclopropanecarbonyl-1,3-cyclohexanedione was used as a starting material, no desired isomerization product was detected even after 1 week. This observation implies that the isomerization may involve a keto-enol tautomerization of 2-acyl group who's the relative stability affects the rate of isomerization. The proposed mechanism of this isomerization is shown in Scheme 4. The first step involves the intrinsic keto-enol tautomerization of the 2-acyl group. The resulting enol oxygen then attacks to the ester carbonyl group to give the tetrahedral carbonyl addition intermediate **6**. Final collapse of **6** generates the isomerized product. In the presence of excess acyl chloride and triethylamine, it undergoes a second esterification to afford the final diester. Several hydrogen–deuterium exchange experiments were performed to gain evidence supporting this isomerization mechanism, as depicted in Scheme 5. First, compound **3i** prepared in Scheme 3 was dissolved in $D_2O$ at room temperature for 24 h. The mixture was then extracted with ethyl acetate, dried in $MgSO_4$, concentrated in vacuo, and purified by column chromatography to give the pure **2e**, which were then subjected to NMR spectroscopic determination. It was




**Scheme 2.**

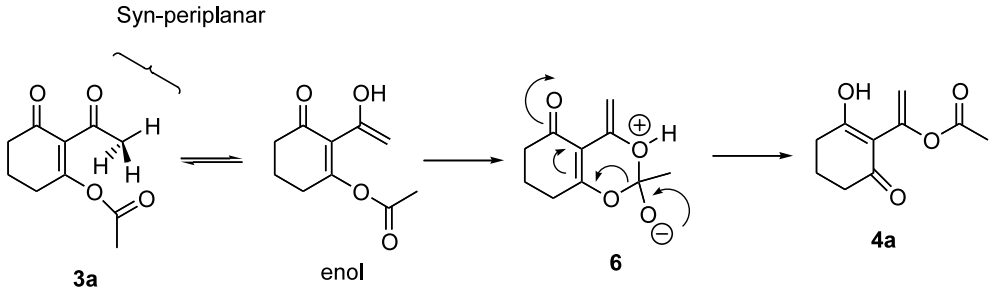



**Scheme 3.**

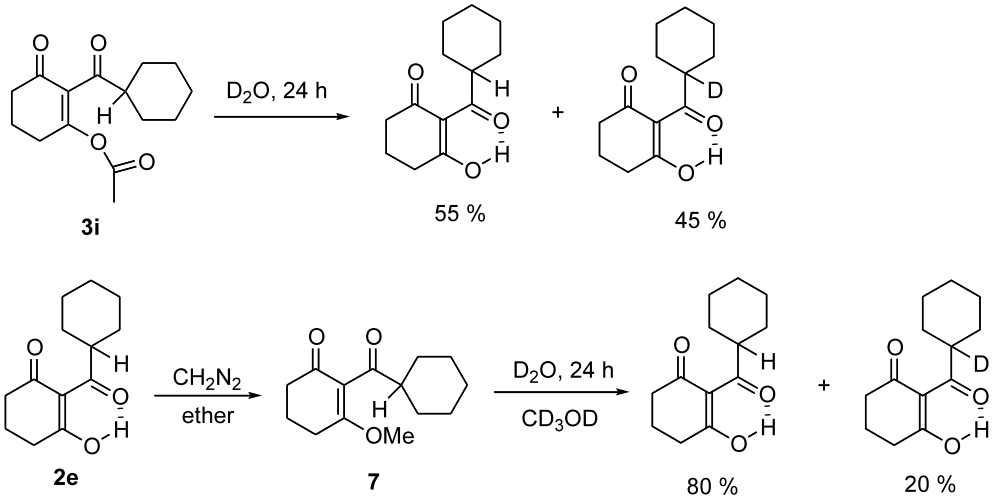
**Table 1.** Reaction yields for the isomerization products **5a–j**

| Entry | Compound | $R_1$ | $R_2$ | $R_3$ | Yield (%)[a] | $Z/E$[b] |
|---|---|---|---|---|---|---|
| 1 | **5a** | H | H | $CH_3$ | 97 | – |
| 2 | **5b** | H | H | $CH(CH_2)_2$ | 85 | – |
| 3 | **5c** | H | $CH_3$ | $CH_3$ | 70 | 4.9/1 |
| 4 | **5d** | H | $CH_3$ | $CH(CH_2)_2$ | 60 | 8.1/1 |
| 5 | **5e** | $CH_3$ | $CH_3$ | $CH_3$ | 55 | – |
| 6 | **5f** | $CH_3$ | $CH_3$ | $CH(CH_2)_2$ | 50 | – |
| 7 | **5g** | H | $C_2H_5$ | $CH_3$ | 30 | 7.3/1 |
| 8 | **5h** | H | $C_2H_5$ | $CH(CH_2)_2$ | 10 | 12.6/1 |
| 9 | **5i** | H | $C_5H_{11}$ | $CH_3$ | <5 | 3/1 |
| 10 | **5j** | H | $C_5H_{11}$ | $CH(CH_2)_2$ | 0 | – |

[a] After column chromatography.
[b] Determined by $^1H$ NMR integration.




**Scheme 4.**




**Scheme 5.**

found that 45% of the hydrogen atom α to 2-acyl carbon of **2e** was exchanged with deuterium, determined by $^1H$ NMR integration using a triplet signal of 4-H at 2.49 ppm as an internal reference of intensity, as shown in Figure 2. In an effort to confirm that the enolization is not solely catalyzed by the product acetic acid presence in the solution during hydrolysis, compound **2e** was methylated by diazomethane and was treated with $D_2O$ under the same condition as **3i**, in this case 20% of the hydrogen atom was found to be exchanged with deuterium. These results indicate that the α-hydrogen on the 2-acyl group of **3i** and **7** can easily undergo keto-enol tautomerization. A control experiment was carried out by using **2e** as a reference compound under the exact same condition, and no detectable hydrogen–deuterium exchange of the 2-acyl α hydrogen was observed.

Although 2-acyl-cyclohexan-1,3-diones have up to 12 possible keto-enol and enol–enol tautomeric forms, recent evidence, which includes X-ray structures[11] and molecular modeling studies,[12] suggests that the C-2 carbonyl moiety of **2** is coplanar and conjugated with the cyclohexene ring system by an intramolecular

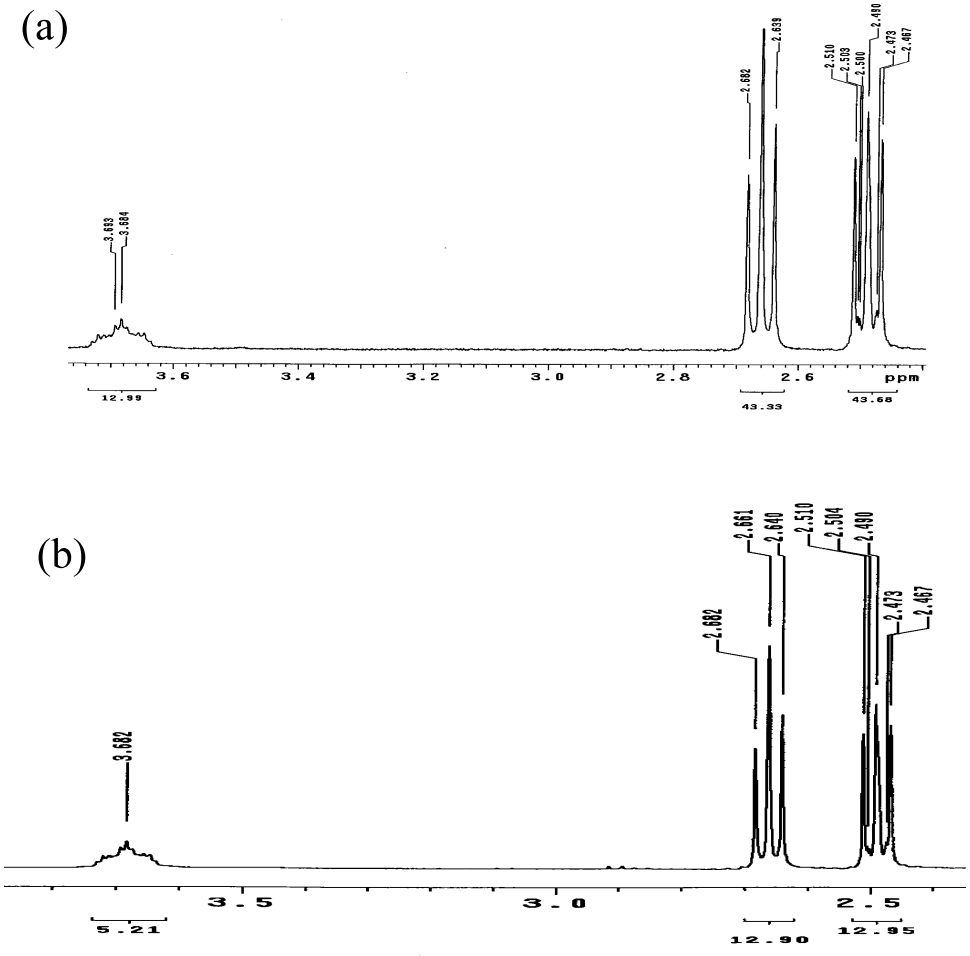
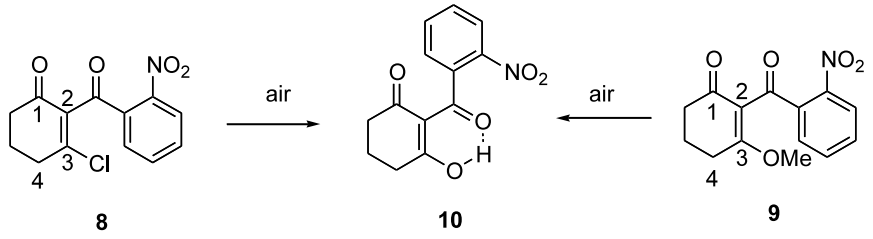



**Figure 2.** Partial $^1$H NMR spectra ($CDCl_3$, 300 MHz) of **3i** and **7** after treatment with $D_2O$. The integration around the absorption at 3.86 ppm in (a) and (b) relative to the triplet signal of 4-H at 2.49 ppm indicates that 45 and 20% of α-hydrogen atom on the acyl group were exchanged by deuterium.

hydrogen bond of the C-3 hydroxyl hydrogen to the oxygen atom of C-2 carbonyl group as indicated in Scheme 2. After esterification of the C-3 hydroxyl group, the intramolecular hydrogen bond of **2** was disrupted and the intrinsic electrostatic repulsion between the 2-acyl oxygen atom and the two 1,3-diketone oxygens caused deformation of **3** from planarity and resulted in their high susceptibility to enolization and subsequent isomerization. Furthermore, molecular modeling studies suggested that there exists a beautiful *syn*-periplanar relationship between the carbonyl group and one of the α-hydrogens in **3** and **7**. Such orientation might make them highly feasible for 2-acyl group to enolize due to the stereoelectronic reason. Thus, we anticipated that this intrinsic electrostatic repulsion perhaps serves as the driving force for **3** to undergo the isomerization reaction. In an effort to obtain further insight into this speculation, we prepared 3-chloro-2-(2-nitrobenzoyl)-1,3-cyclohexadien-1-ol (**8**) and 3-methoxy-2-(2-nitrobenzoyl)-2-cyclohexen-1-one (**9**) from 3-hydroxy-2-(2-nitrobenzoyl)cyclohex-2-en-1-one (**10**) and examined their stability under ambient temperature. It was found that both **8** and **9** slowly decomposed back to **10** even when stored at −20°C with or without solvent, as depicted in Scheme 6. On the basis of the outcome of this model study, the dipolar repulsions




**8** **10** **9**

**Scheme 6.**

between the C-2 carbonyl group and the C-1 carbonyl group as well as the C-3 oxygen or chlorine atom apparently rendered **8** and **9** in an unfavorable high energy status. Since **8** and **9** can not undergo isomerization like **3**, they react instead with moisture in the air via a nucleophilic 1,4-addition and then subsequent elimination reaction to regain the planar structure and intramolecular hydrogen bonding.

In summary, the factors affecting the rate of the isomerization of enol esters derived from 2-acyl-1,3-cyclohexanediones and its mechanism were investigated. The results suggest the isomerization involves the intrinsic keto-enol tautomerization, follows by intramolecular attack of the enol oxygen to ester carbonyl group. The driving force for this migration is likely that the intrinsic electrostatic repulsion between the 2-acyl oxygen atom and the two 1,3-diketone oxygens caused deformation of enol esters from planarity and resulted in their high susceptibility to isomerization.

## Acknowledgements

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10. All new compounds exhibited satisfactory $^{1}H$ and $^{13}C$ NMR, IR, and low and high resolution mass spectroscopic data for the indicated structures. Representative procedure for preparation of **5a–j**: To a solution of 2-acetyl-3-hydroxy-2-cyclohexenone (**2a**, 100 mg, 0.65 mmol) in methylene chloride (5 mL) was added acetyl chloride (127 mg, 1.62 mmol) and $Et_3N$ (177 mg, 1.75 mmol). After completion of the reaction (monitored by TLC), water (5 mL) was added to the mixture and the product was extracted twice with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (EtOAc: hexanes = 4:6) to give a light brown liquid of 2-[1-(methylcarbonyloxy)-1-ethenyl]-3-(methylcarbonyloxy)-2-cyclohexen-1-one (**5a**) with a 97% yield. $^{1}H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 5.20 (d, $J = 1.8$ Hz, 1H), 4.94 (d, $J = 1.8$ Hz, 1H), 2.50 (t, $J = 6.3$ Hz, 2H), 2.23 (s, 3H), 2.09 (s, 3H), 2.06 (quintet, $J = 6.3$ Hz, 2H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 196.0, 168.4, 167.6, 167.0, 143.8, 125.4, 108.4, 37.1, 28.9, 20.8, 20.8, 20.2. IR (KBr) $\nu$ 1769, 1682, 1635 (C=O), 1208, 1158 ($CH_2$=C-O) $cm^{-1}$. HRMS: calcd for $C_{12}H_{14}O_5$, 238.2420, found 238.2435.
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