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Synthesis of α-hydroxy-γ-butyrolactones from acrylates and 1,3-dioxolanes using *N*-hydroxyphthalimide (NHPI) as a key catalyst

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Abstract—A new route to α-hydroxy-γ-butyrolactones through three-component radical coupling of 1,3-dioxoranes, acrylates, and molecular oxygen using *N*-hydroxyphthalimide (NHPI) as a key catalyst has been developed. For example, the addition of 1,3-dioxarane to methyl acrylate under dioxygen by NHPI followed by catalytic hydrogenation of the resulting adduct on Pd/C afforded α-hydroxy-γ-butyrolactone in good yield. This method provides a facile approach to α-hydroxy-γ-butyrolactones, which are difficult to synthesize by conventional methods.
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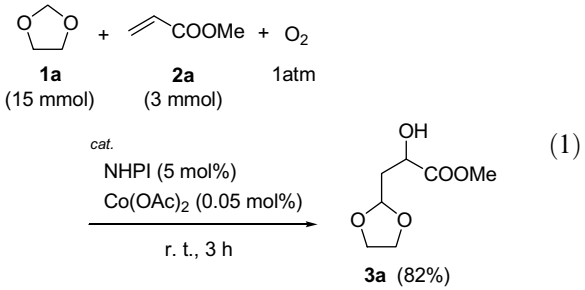
α-Hydroxy-γ-butyrolactone derivatives are important starting materials in pharmaceutical synthesis and are prepared by various methods. For instance, (*S*)-α-hydroxy-γ-butyrolactone is prepared from ephedrine-derived morpholinedione[1] and homoserine.[2] Malic acid is used as the starting material for the synthesis of asymmetric α-hydroxy-γ-butyrolactone as a transient intermediate for the synthesis of various pharmaceuticals.[3] Recently, we have reported that the concomitant catalytic radical addition of 1,3-dioxolane (**1a**), synthetic equivalent of formaldehyde, and molecular oxygen to methyl acrylate (**2a**) leading to 2-hydroxy-4-(1,3-dioxolan-2-yl)valerate (**3a**) is efficiently catalyzed by *N*-hydroxyphthalimide (NHPI) (Eq. 1).[4]



(1)

The adduct **3a** is an interesting compound which can be used as starting material for the synthesis of α-hydroxy-γ-butyrolactone (**6a**), since it is easily converted into the 2,5-dihydroxypentanoic acid (**5a**) through aldehyde **4a** by the deprotection of **3a** with acid followed by hydrogenation. The intramolecular cyclization of **5a** would provide **6a**. The merit of the present method is that **3a** is very easily prepared by the use of cheap **1a** and **2a**, which are manufactured in large scale as bulk chemicals. Thus, we have tried to develop a new synthetic route to α-hydroxy-γ-butyrolactones from 1,3-dioxoranes and acrylates by the use of NHPI as a key catalyst.

At first, **3a** was prepared according to a previous report. The reaction of **1a** (15 mmol) with **2a** (3 mmol) under O_2 catalyzed by NHPI (0.15 mmol) and $Co(OAc)_2$ (0.0015 mmol) without any solvent at room temperature for 3 h produced **3a** in 82% isolated yield based on **2a** used. **1a** was found to be recovered unchanged. But, when the amount of **1a** used was halved, **3a** was difficult to be obtained with satisfactory yield.

Since the direct deprotection of **3a** with dilute sulfuric acid to aldehyde **4a** was difficult to carry out, **3a** was treated in methanol in the presence of *p*-toluenesulfonic acid (TsOH) followed by treatment of the resulting dimethyl acetal **3a**′ in aqueous acetic acid to give aldehyde **4a** in quantitative yield. Representative results for the conversion of adduct **3a** into dimethyl acetal **3a**′ are shown in Table 1.

Keywords: α-Hydroxy-γ-butyrolactone; 1,3-Dioxoranes; Acrylates; Dioxygen; N-Hydroxyphthalimide.
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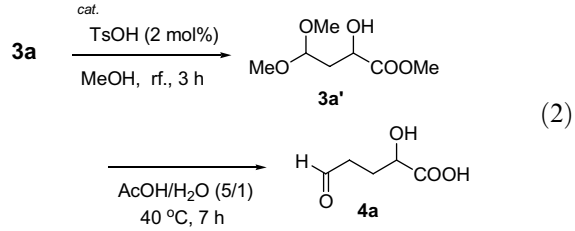
Table 1. Deprotection of adduct **3a** to dimethyl acetal **3a′** under several conditions[a]

Run	MeOH/mL	TsOH/mol%	Temp/°C	Yield/%
1	1.5	0.5	40	28
2	1.5	0.5	Reflux	75
3	5	2.0	Reflux	Quant.

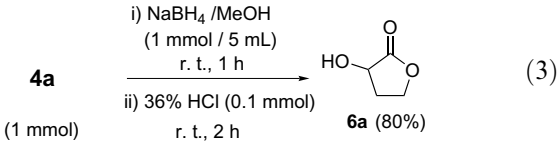
[a] Adduct **3a** (1 mmol) was reacted in MeOH in the presence of TsOH for 3 h.

The reaction of **3a** (1 mmol) in methanol (5 mL) in the presence of TsOH (2 mol%) under reflux afforded dimethyl acetal **3a′** in quantitative yield (run 3). When the quantities of methanol and TsOH were reduced, **3a** was difficult to be transformed to **3a′** completely (runs 1 and 2). The deprotection of **3a′** to aldehyde **4a** was successfully achieved by treating with a mixed solvent of acetic acid (5 mL) and water (1 mL) at 40 °C for 7 h (Eq. 2).



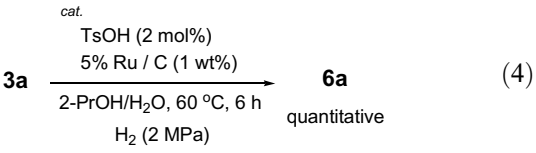
(2)

We next tried the conversion of **4a** to hydroxyl lactone **6a**. When **4a** was treated with $NaBH_4$ in methanol followed by aq HCl, it was found that the reduction of **4a** and the intramolecular cyclization of the resulting alcohol **5a** simultaneously take place in one-pot to give **6a** in 80% yield (Eq. 3).



(3)

Although it was found that **6a** can be synthesized from cheap starting materials, this strategy consisting of four-step transformations is troublesome and not suited for large-scale synthesis. Thus, the direct conversion of **3a** into **6a** by the reductive deprotection of dioxorane moiety by H_2 on Ru/C or Pd/C was examined under several conditions. After isolation of **3a** from the reaction mixture, the **3a** (1 mmol) was hydrogenated in 2-propanol (1.5 mL) and H_2O (1.5 mL) involving *p*-toluenesulfonic acid (TsOH) (75 mg) under H_2 (2 MPa) on 5%Ru/C (1 wt%) at 60 °C for 6 h to afford α-hydroxy-γ-butyrolactone **6a** in quantitative yield (Eq. 4).



(4)

The same result was obtained by the use of 10%Pd/C (1 wt%) in the place of 5%Ru/C.

Table 2. One-pot synthesis of **6a** upon treatment of reactant derived from **1a** and **2a** with H_2 on Pd/C[a]

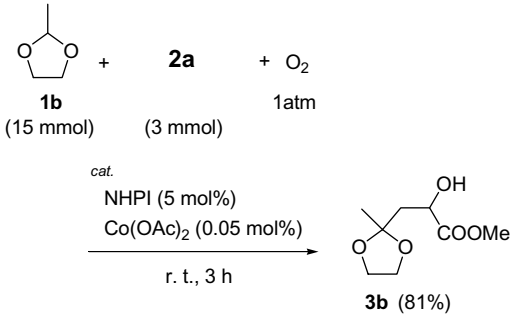
Run	Cat. (wt%)	H_2 (MPa)	**6a**/%
1	5% Pd/C (5)	8	0
2	5% Pd/C (5)	8	86
3	10% Pd/C (10)	8	93

[a] See text.

From a practical synthetic viewpoint, the one-pot synthesis of **6a** without isolation of **3a** is more attractive in large-scale synthesis. Thus, a reaction mixture obtained by the reaction of **1a** with **2a** under the condition of Eq. 1 was hydrogenated with H_2 (8 MPa) on 10%Pd/C (5 wt%), but **6a** was not obtained at all (Table 2, run 1). To reveal the reason for unsuccessful performance of the hydrogenation, the iodometry of the resulting products was examined, and it was found that small amounts of certain peroxides are involved in the reaction products probably because of the reaction of **1a** with **2a** at room temperature without solvent. These peroxides are thought to deactivate the Pd/C catalyst. Hence, the reaction mixture was evaporated under reduced pressure to remove the unreacted **1a** and was treated in 2-propanol in the presence of TsOH at 70 °C for 6 h followed by hydrogenation on 5%Pd/C (5 wt%) under H_2 (8 MPa) at 60 °C for 6 h to afford **6a** in 86% yield (run 2). When 10%Pd/C (10 wt%) was employed, **6a** was obtained in 93% yield (run 3). These results show that the peroxides containing in the crude products are decomposed in 2-propanol by heating at 70 °C.

The success of the one-pot synthesis of **6a**, which is an important raw material in pharmaceutical synthesis, from cheap bulk chemicals, **1a** and **2a**, provides a very convenient method for large-scale synthesis.

We next examined the reaction of 2-methyl-1,3-dioxolane (**1b**) (15 mmol) with **2a** (3 mmol) in the presence of NHPI and $Co(OAc)_2$ without any solvent at room temperature for 3 h to lead to 2-hydroxy-4-methyl-4-(1,3-dioxolan-2-yl)valerate (**3b**) in 81% yield based on **2a** (Eq. 5).



(5)

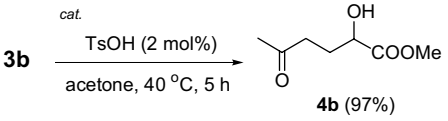
The treatment of **3b** with TsOH afforded a deprotected product, methyl 2-hydroxy-5-oxahexanoate (**4b**), in quantitative yield (Eq. 6).

It was found that the hydrocyclization of **4b** to 4-methyl-2-hydroxy-γ-butyrolactone (**6b**) is important to carry out in basic media. Table 3 shows the hydrocycli-

Table 3. Hydrocyclization of **4b** under several conditions[a]

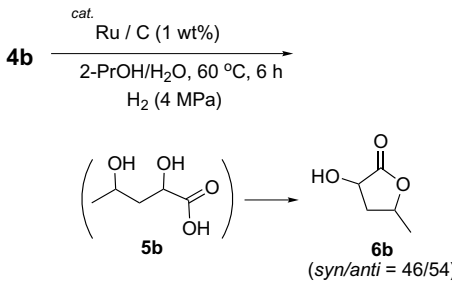
Run	Cat. (wt%)	**6b**/% (*syn*/*anti*)
1	5% Ru/C (1)	68 (53/47)
2[b]	5% Ru/C (1)	43 (40/60)
3[c]	5% Ru/C (1)	95 (46/54)
4	5% Ru/Al_2O_3 (1)	99 (42/58)
5	5% $Pd/CaCO_3$ (1)	95 (42/58)
6	Raney Ni (5)	93 (47/53)

[a] Compound **4b** (1 mmol) was treated with H_2 (4 MPa) in 3-propanol/H_2O (3/3 mL) at 60 °C for 6 h.
[b] Aq HCl (0.1 mL) was added.
[c] KOH (0.01 mmol) was added.



(6)

zation of **4b** in several catalysts varying media. When **4b** was allowed to react with H_2 (4 MPa) on Ru/C in basic 2-propanol containing in a small amount of KOH, the hydrogenation of **4b** followed by intramolecular cyclization of the resulting alcohol **5b** concomitantly took place in one-pot to form a stereoisomeric mixture of *syn*- and *anti*-4-methyl-2-hydroxy-γ-butyrolactones (*syn*-**6b** and *anti*-**6b**)[5] in 95% yield (Eq. 7, Table 3, run 3). However, the same reaction in 2-propanol acidified by aq HCl gave a complex mixture involving *syn*-**6b** and *anti*-**6b** in low yields (run 2). However, the hydrocyclization was found to be induced in basic media involving KOH (run 3).



(7)

The hydrocyclization of **4b** proceeds smoothly on Ru and Pd supported on basic oxides like Al_2O_3 and $CaCO_3$ (runs 4 and 5). Therefore, inherent basic Raney Ni catalyst was also effective for the present reaction (run 6).

In conclusion, we have developed the one-pot synthetic method of α-hydroxy-γ-butyrolactone **6a** from cheap starting materials, 1,3-dioxorane **1a** and methyl acrylate **2a**, which are easily available from commercial source, using NHPI as a key catalyst. This method was successfully extended for the synthesis of methyl substituted α-hydroxy-γ-butyrolactone **6b** from 2-methyl-1,3-dioxolane **1b** and **2a**.

Acknowledgements

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References and notes

1. Pansare, S. V.; Shinkre, B. A.; Bhattacharyya, A. *Tetrahedron* **2002**, *58*, 8985–8991.
2. Kenne, L.; Unger, P.; Wehler, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1183–1186.
3. (a) Schinzer, D.; Bauer, A.; Schieber, J. *Chem. Eur. J.* **1999**, *5*, 2492–2500; (b) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129–9142; (c) Phukan, P.; Sasmal, S.; Maier, M. E. *Eur. J. Org. Chem.* **2003**, 1733–17400; (d) Mulzer, J.; Mantoulidis, A.; O'hler, E. *J. Org. Chem.* **2000**, *65*, 7456–7467; (e) Buser, H. P.; Pugin, B.; Spindler, F.; Sutter, M. *Tetrahedron* **1991**, *47*, 5709–5716; (f) Shiuey, S.-J.; Partridge, J. J.; Uskokovic', M. R. *J. Org. Chem.* **1988**, *53*, 1040–1046; (g) Green, D. L. C.; Kiddle, J. J.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 2865–2874.
4. Hirano, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 2457–2458.
5. The products, *syn*-**6b** and *anti*-**6b**, were identified through the comparison of the ^{13}C NMR spectral data of the isolated products with that reported in the literature: Blandin, V.; Carpentier, J.-F.; Mortreux, A. *Eur. J. Org. Chem.* **1999**, 1787–1793.