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Catalytic Hydrogenation of α,*β*-Epoxy Ketones to Form *β*-Hydroxy Ketones Mediated by an NADH Coenzyme Model

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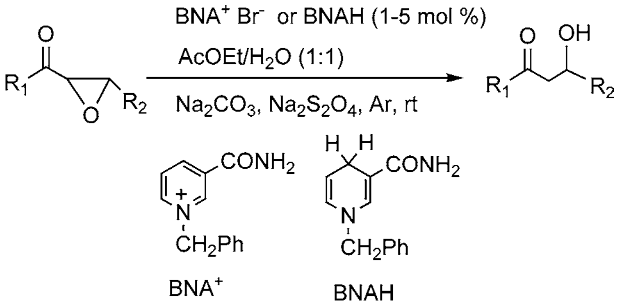
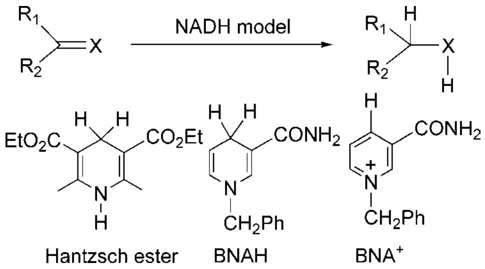
ABSTRACT



The hydrogenation of α,*β*-epoxy ketones can be mediated by a catalytic amount of BNAH or BNA$^+$Br$^-$ to form corresponding *β*-hydroxy ketones in high yield. $Na_2S_2O_4$ is used as the reducing agent to convert BNA$^+$Br$^-$ to BNAH. A radical mechanism has been proposed to understand many observations of this catalytic reaction.

The NAD$^+$/NADH coenzyme couple-mediated hydrogenation reactions (Scheme 1) are ubiquitous in biological systems.[1] There is a great interest in utilizing the coenzyme couple in organic synthesis. Hantzsch ester and 1-benzyl-1,4-dihydronicotinamide (BNAH) are common models of NADH.[2] These models are known to reduce aldehydes, ketones, and activated olefins.[3−5] Recently, Hantzsch ester, accompanied with some small-molecule organocatalysts, was used in hydrogenation of α,*β*-unsaturated aldehydes,[6] imines,[7] and α,*β*-epoxy ketones.[8] These reactions are of great importance in organic synthesis and are attracting increasing attention.[9] However, these procedures all require the use of a stoichiometric amount of the NADH model compound. It would be desirable to carry out the reactions using a catalytic

Scheme 1



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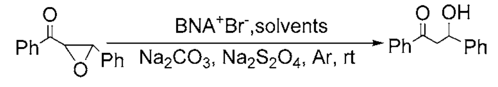
amount of NADH models.[10] Very recently, Imada et al. reported a hydrogenation of olefins catalyzed by Flavin, another redox coenzyme.[11] In this communication, we wish to report on our preliminary results using a catalytic amount (1−5 mol %) of BNA^+Br^- or BNAH to mediate the hydrogenation of α,*β*-epoxy ketones to form *β*-hydroxy ketones in excellent yields.

Initial experiments were concentrated on the selection of the solvent and other conditions for the hydrogenation of **1a** in Table 1. As shown, several solvents were employed. A mixed organic/water solvent is necessary for the reaction because of the presence of both neutral aromatic and ionic species. Water or ethanol/water (1:1) gave very poor conversion (Table 1, entries 1 and 2). However, both $MeCN/H_2O$ (1:1) and $AcOEt/H_2O$ (1:1) gave complete conversion and high isolated yields.[12] The latter solvent condition was chosen for further studies in consideration of the environmental cause.

Table 1. Optimization of Solvent and Other Conditions



1a **2a**

entry	solvents	BNA^+Br^- (mol %)	time (h)	conversion (%)	isolated yield (%)
1	H_2O	5	40	<10	2
2	$EtOH/H_2O$ (1:1)[a]	5	40	<10	2
3	$MeCN/H_2O$ (1:9)	5	48	60	40
4	$MeCN/H_2O$ (1:1)	5	26	100	91
5	$AcOEt/H_2O$ (1:9)	5	48	60	35
6	$AcOEt/H_2O$ (1:1)	5	26	100	93
7	$AcOEt/H_2O$ (1:1) ($h\upsilon$)[b]	5	2	100	91
8	$AcOEt/H_2O$ (1:1) ($h\upsilon$)[b]	1	16	100	90
9	$AcOEt/H_2O$ (1:1) ($h\upsilon$)[b]	0.2	40	90	60

[a] Volume ratio. [b] Irradiation with a 450 W high-pressure mercury lamp (λ > 300 nm).

Other reaction conditions were also studied. When the reaction temperature was raised from room temperature to 60 °C, the reaction time could be reduced to about 2 h. However, the yield of **2a** was drastically decreased to about 30% due to increased formation of byproducts. We then tested the effect of irradiation with a high-pressure mercury lamp and found that the reaction was significantly accelerated. The reaction completed in 2 h, and **2a** was formed in about 91% yield (Table 1, entry 7). When BNA^+Br^- was reduced to 1 mol %, the reaction time had to be increased to about 16 h, again with about 90% isolated yield (entry 8). When BNA^+Br^- was further reduced to 0.2 mol %, however, only 60% of **2a** was isolated after 40 h (entry 9).

A series of 16 α,*β*-epoxy ketones were then investigated with and without irradiation using 5 mol % of BNA^+Br^-. In all cases where R_1 was an aromatic ring, complete conversion and high yields (90−94%) were obtained as shown in Table 2 (**1a**−**o**). The yield is somewhat reduced when R_1 is a methyl group (**1p**, 80%). Irradiation significantly reduces the reaction time but only has a minor effect on the yield. These results indicate a general feasibility of the reaction.

All above reactions were conducted under argon. No reaction was observed (starting material was recovered) in an oxygen-saturated solution regardless of whether the reaction was under irradiation. Both BNA^+Br^- and BNAH work equally well, indicating a fast turnover of the redox couple. On the basis of these observations and by reference to the literature,[8,13] we propose a radical mechanism for the reaction, as shown in Scheme 2.[14]

In the present reaction, BNA^+ is first transformed into 1-benzyl-1,4-dihydronicotinamide (BNAH) by the reducing agent $Na_2S_2O_4$.[14] BNAH gives an electron to the α,*β*-epoxy ketone to form an anionic radical **3** and $BNAH^{+\bullet}$. A radical ring-opening reaction regioselectively converts **3** into **4**.[15]

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(11) Fish et al. reported the regeneration of NADH models using the strategy of regioselective reduction of NAD^+ models with the $[Cp^*Rh(bpy)H]^+$ transition-metal catalyst: Lo, H. C.; Buriez, O.; Kerr, J. B.; Fish, R. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1429−1432.

(12) It appears that the mixed solvent increases the reactivity of BNAH with an α,*β*-epoxy ketone considerably because in CH_3CN solvent BNAH and a Hantzsch ester do not react with an α,*β*-epoxy ketone even under elevated temperatures (also see ref 8). It is possible that a better solubility for the $Na_2SO_4/Na_2CO_3/BNA^+Br^-$ system in a mixed solvent also contributes to the increased reaction rate.

(13) For a recent review on the mechanisms of NAD^+/NADH-mediated hydrogenations, see: Gebicki, J.; Marcinek, A.; Zieloka, J. *Acc. Chem. Res.* **2004**, *37*, 379−386.

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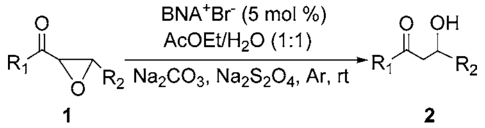
Table 2. Hydrogenation of α,*β*-Epoxy Ketones to *β*-Hydroxy Ketones



			isolated yield (%)	
substrate	R1	R2	*a*	*b*
1a	Ph	Ph	**2a** (93)	**2a** (91)
1b	Ph	4-Me-C_6H_4	**2b** (91)	**2b** (90)
1c	Ph	4-MeO-C_6H_4	**2c** (90)	**2c** (90)
1d	Ph	4-Cl-C_6H_4	**2d** (94)	**2d** (92)
1e	Ph	2-MeO-C_6H_4	**2e** (91)	**2e** (89)
1f	Ph	2-Cl-C_6H_4	**2f** (92)	**2f** (90)
1g	4-Me-C_6H_4	Ph	**2g** (90)	**2g** (88)
1h	4-MeO-C_6H_4	Ph	**2h** (90)	**2h** (87)
1i	4-F-C_6H_4	Ph	**2i** (94)	**2i** (92)
1j	4-Br-C_6H_4	Ph	**2j** (93)	**2j** (92)
1k	4-Cl-C_6H_4	Ph	**2k** (93)	**2k** (91)
1l	2-furyl	Ph	**2l** (92)	**2l** (93)
1m	2-thienyl	Ph	**2m** (91)	**2m** (93)
1n	2-naphthyl	Ph	**2n** (91)	**2n** (90)
1o	4-biphenyl	Ph	**2o** (90)	**2o** (88)
1p	Me	Ph	**2p** (80)	**2p** (72)

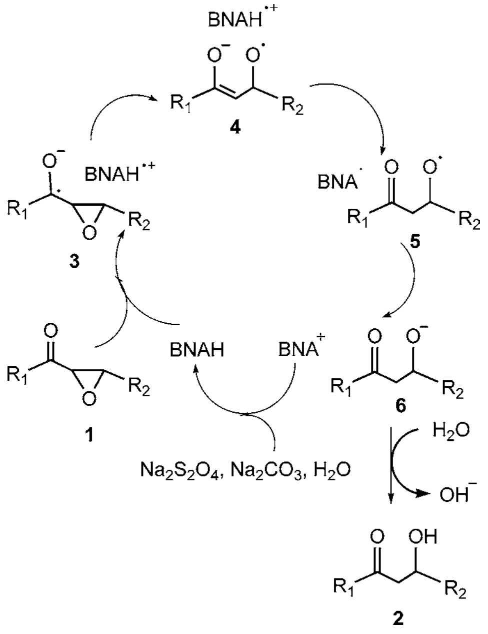
[a] With room light, 24−28 h, 100% conversion. [b] With a 450 W mercury lamp, 2−3 h, 100% conversion.

A proton transfer from BNAH$^{+\bullet}$ to **4** followed by an enol/keto tautomerization results in the formation of **5** and BNA$^\bullet$. An electron transfer from BNA$^\bullet$ to **5** results in the formation of **6** and the regeneration of BNA$^+$. The reaction is completed with the protonation of **6** by water.[16]

This mechanism explains why the presence of O_2 suppresses the reaction because O_2 is a radical trapper and it prevents the electron transfer from BNAH to **1** to generate **3** and BNAH$^{+\bullet}$. It is in accord with the observed specific C_α−O bond cleavage. The mechanism also accommodates the observed rate acceleration by irradiation. Because we used a Pyrex flask (λ > 300 nm) for the photoirradiation experiment, the compound that absorbs light is presumed to be BNAH (λ_{max} = 380 nm).

We find that Hantzsch ester cannot be used for the catalytic reaction. After the first cycle, Hantzsch ester is converted into substituted pyridine, which cannot be converted back into Hantzsch ester under the present reaction conditions. However, we have found that N-methylated Hantzsch ester, which is analogues to BNAH, can mediate the current reaction as efficiently as BNAH.

Scheme 2. Proposed Mechanism for the Hydrogenation of α,*β*-Epoxy Ketones to *β*-Hydroxy Ketones Mediated by BNA$^+$Br$^-$



In summary, we have found an efficient catalytic version of hydrogenation of α,*β*-epoxy ketones to form corresponding *β*-hydroxy ketones using a BNAH (BNA$^+$Br$^-$) catalyst. To the best of our knowledge, this is the first example of catalytic hydrogenation mediated by an NAD$^+$/NADH coenzyme model. We are currently exploring the application of the strategy in other reactions.

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Supporting Information Available: Characterization data (IR, NMR, MS) for all the prepared *β*-hydroxy ketones. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Because the ketyl anion radical **3** has a resonance form with a radical on oxygen and an anion on carbon, it is also possible that **3** undergoes an anion-induced ring opening to give **4** with an enol radical and an oxygen anion. This process is probably less preferred because the enolate form of **4** as shown in Scheme 2 is likely more stable.

(16) The reaction solution actually becomes slightly less basic because the conversion of BNA$^+$Br$^-$ to BNAH by $Na_2S_2O_4$ generates acid.