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PAA-supported Hantzsch 1,4-dihydropyridine ester: an efficient catalyst for the hydrogenation of α , β -epoxy ketones

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ABSTRACT

A new type of water-soluble polymer-supported NADH co-enzyme model-PAA (polyacrylic acid)-supported Hantzsch 1,4-dihydropyridine ester (PAA–HEH) was designed and synthesized. Catalytic amount of the supported reagent was used in the hydrogenation of α , β -epoxy ketones to the corresponding β -hydroxy ketones and showed great catalytic efficiency in the reduction reaction. This PAA–HEH was an optimal potential for recycling use.

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NAD(P)H co-enzyme is a kind of oxidoreductase co-enzyme with great importance.¹ It participates in more than 400 kinds of important biological redox reactions in vivo. NAD(P)H coenzyme is also a kind of natural organic hydride compound.² Based on the active core, 1,4-dihydropyridine ring, of NAD(P)H, a series of model compounds have been synthesized to mimic the reductive performance of NADH coenzyme in vitro, such as BNAH, HEH, and AcrH₂.³ Some of these models synthesized, like Hantzsch ester, accompanied with some small-molecule organocatalysts, were applied in the reductive reactions of aldehydes, ketones, activated olefins, and the hydrogenation of β -unsaturated aldehydes, α,β epoxy ketones, imines, and showed great reductive activities and selectivities.⁴ However, the separating operation of these reactions is complicated. To simplify the separation process and promote the extensive use of the models, they have been immobilized on the surface of some supports, which combines the advantages of both the models and the supports.⁵ In the past few decades, the supports of the NADH coenzyme model compounds have experienced the Merrifield resin,⁶ SiO₂,⁷ polysiloxane,⁸ water-soluble polymer like PEG,⁹ ferrocene,¹⁰ carbon nanotubes,¹¹ magnetic nano like Fe₃O₄,¹² graphene,¹³ etc.

Considering our group's experience in the synthesis, application, and characterization of NADH coenzyme model compounds, herein we chose Hantzsch 1,4-dihydropyridine ester as the co-enzyme model and water-soluble polymer polyacrylic acid (PAA) as the support and they were connected to form a novel water-soluble polymer-supported reagent. ¹⁴ The synthesis of the PAA-supported Hantzsch ester is presented herein as well as the application of the reagent in the hydrogenation of the α , β -epoxy ketones in homogeneous reaction system.

Polyacrylic acid-supported Hantzsch ester was synthesized according to the following protocol (Scheme 1). PAA was directly purchased and the Hantzsch 1,4-dihydropyridine ester was prepared according to the literature.¹⁵ HEH was co-valently connected with the carboxyl group of PAA through amide bond. Firstly, the mixture of formaldehyde, ethyl acetoacetate, and ammonium acetate was dissolved in ethanol and refluxed then to get Hantzsch 1,4-dihydropyridine ester. At the same time, the polyacrylic acid 3000 was treated with thionyl dichloride in DMF to obtain the corresponding partly chloride-PAA, which was then refluxed with the Hantzsch ester synthesized in DMF to get the PAA-partly-supported Hantzsch ester which was a light milky solid at room temperature and could be dissolved in water easily. The supported-reagent was characterized by elemental analysis and the loadings of PAA-HEH were 0.34 mmol/g.

To examine the reducibility and application of the PAA–HEH, we herein present the use of the supported-reagent in the reduction of a series of α , β -epoxy ketones. According to our previous work,¹⁶ all of the reactants including the phenyl(3-phenyloxi-ran-2-yl)methanone, the supported-reagent, Na₂S₂O₄ (3 equiv), Na₂CO₃ (5 equiv) were mixed together and dissolved in mixed AcOEt/H₂O (v:v = 1:1) solvent in one tube. The solution was irradiated with a 450 W high-pressure mercury lamp at room tem-







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Scheme 1. The synthetic protocol of the PAA-HEH.

Table 1 The hydrogenation of $\alpha,\beta\text{-epoxy}$ ketones to $\beta\text{-hydroxy}$ ketones a





(continued on next page)

Table 1 (continued)



^a Compound **1** (0.2 mmol), Na₂S₂O₄ (0.6 mmol), Na₂CO₃ (1.0 mmol), and PAA–HEH (0.01 mmol) were dissolved in 2 mL of AcOEt/H₂O (1:1). The solution was irradiated with a 450 W mercury lamp (λ >320 nm) under an argon atmosphere at room temperature for 12 h. ^b Isolated yields.

Table 2

Reducibility of the PAA-HEH after recycling



^a Compound **1** (0.2 mmol), Na₂S₂O₄ (0.6 mmol), Na₂CO₃ (1.0 mmol), and PAA– HEH (0.01 mmol) were dissolved in 2 mL of AcOEt/H₂O (1:1). The solution was irradiated with a 450 W mercury lamp (λ >320 nm) under an argon atmosphere at room temperature for 12 h.

^b See references and notes.¹⁷

perature. And the reaction must be conducted under an argon atmosphere. After being stirred for 12 h, the reaction was completed and phenyl(3-phenyloxiran-2-yl)methanone was reduced to the corresponding 3-hydroxy-1,3-diphenyl-propan-1-one in satisfactory yield.

We then explored the use of this new PAA-supported NADH model in the hydrogenation of a variety of α , β -epoxy ketones and the results are summarized in Table 1. In general, good yields of β -hydroxy ketones derived from α , β -epoxy ketones were observed in Table 1, indicating that this new NADH model possesses strong reducibility. The results obtained showed that, in general, when R₁ was the aromatic ring or the heteroaromatic ring, the substrates could be reduced to the corresponding β -hydroxy ketones in good yields (**2a–2r**), showing that steric effect was not clearly visible. But the reaction resulted in a low conversion when R₁ was a methyl group (**2s**). We believe that the reaction goes through a radical ring-opening mechanism. When R₁ was aromatic substituents, the intermediate of ring-opening would be more stable than alkyl substituents. So the yield of the product reduced when R₁ was an alkyl substituent.

However, no reaction was observed when the same system was performed with active alkenes containing nitrile groups. All of the alkenes were hydrolyzed before they were reduced.

A series of experiments of the hydrogenation of 4-chlorophenyl-3-phenyloxiran-2-yl-methanone to the corresponding 1-(4-chlorophenyl)-3-hydroxy-3-phenylpropan-1-one (**2m**) was carried out to measure the recycling performance of the supported reagent (Table 2). It was shown that the reducibility of the PAA– HEH obtained through dialysis separation decreased slightly after being reused at least 5 times.

In summary, we have developed a new type of water-soluble polymer-supported organic hydride compound—PAA-supported Hantzsch 1,4-dihydropyridine ester. Catalytic amount of the supported reagent was used in the hydrogenation of α , β -epoxy ketones to obtain the corresponding β -hydroxy ketones and showed great reducibility after being reused for at least 5 times. We are now working on the application of the supported reagent in other reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013. 07.112. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

- Westheimer, F. H. In *Pyridine Nucleotide Coenzyme, Part A*; Dolphin, D., Poulson, R., Avramovic, O., Eds.; Wiley-Interscience: New York, 1988; p 253.
- Zhu, X. Q.; Zhang, M. T.; Yu, A.; Wang, C. H.; Cheng, J. P. J. Am. Chem. Soc. 2008, 130, 2501–2516.
- (a) Murakami, Y.; Kikuchi, J. I.; Hisaeda, Y.; Hayashida, O. Chem. Rev. 1996, 96, 721–758; (b) Stout, D. M.; Meyers, A. I. Chem. Rev. 1982, 82, 223–243.
- 4 For selected examples on applications of NADH models see: (a) Fukuzumi, S.; Ish-ikama, M.; Tanaka, T. Tetrahedron 1984, 42, 1021-1034; (b) Gelbard, G.; Lin, J.; Roques, N. J. Org. Chem. 1992, 57, 1789-1793; (c) Kanomata, N.; Suzuki, M.; Yoshida, M.; Nakata, T. Angew. Chem., Int. Ed. 1998, 37, 1410-1412; (d) Mikata, Y.; Hayashi, K.; Mizukami, K.; Matsumoto, S.; Yano, S.; Yamazaki, N.; Ohno, A. Tetrahedron Lett. 2000, 41, 1035-1038; (e) Tanner, D. D.; Singh, H. K.; Kharrat, A.; Stein, A. R. J. Org. Chem. 1987, 52, 2142-2146; (f) Tanner, D. D.; Stein, A. R. J. Org. Chem. 1988, 53, 1642-1646; (g) Fukuzumi, S.; Mochizuki, S.; Tanaka, T. J. Am. Chem. Soc. 1989, 111, 1497-1499; (h) Zhu, X. Q.; Liu, Y. C. J. Org. Chem. 1998, 63, 2786-2787; (i) Li, J.; Liu, Y. C.; Deng, J. G. Tetrahedron: Asymmetry 1999, 10, 4343-4347; (j) Li, J.; Liu, Y. C.; Deng, J. G.; Li, X. Z.; Cui, X.; Li, Z. Tetrahedron: Asymmetry 2000, 11, 2677-2682; (k) Lee, H. W.; Kim, B. Y.; Ahn, J. B.; Son, H. J.; Lee, J. W.; Ahn, S. K.; Hong, C. I. Heterocycles 2002, 57, 2163-2173; (1) Torchy, S.; Cordonnier, G.; Barbry, D.; Eynde, J. J. V. Molecules 2002, 7, 528-533; (m) Zhang, Z.; Gao, J.; Xia, J.-J.; Wang, G.-W. Org. Biomol. Chem. 2005, 3, 1617-1619; (n) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. Angew. Chem., Int. Ed. 2004, 43, 6660-6662; (o) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. Angew. Chem., Int. Ed. 2005, 44, 108-110; (p) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. J. Am. Chem. Soc. 2005, 127, 32-33; (q) Liu, Z.; Han, B.; Liu, Q.; Zhang, W.; Yang, L.; Liu, Z. L.; Yu, W. Synlett 2005, 1579-1580; (r) Liu, Z.; Liu, Q.; Zhang, W.; Mu, R.; Yang, L.; Liu, Z. L.; Yu, W. Synthesis 2006, 771-774; (s) Hoffmann, S.; Seayad, A. M.; List, B. Angew. Chem., Int. Ed. 2005, 44, 7424-7427; (t) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. Org. Lett. 2005, 7, 3781-3783; (u) Rueping, M.; Azap, C.; Sugiono, E.; Theissmann, T. Synlett 2005, 15, 2367-2369; (v) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. J. Am. Chem. Soc. 2006, 128, 84-86; (w) Zhang, J.; Jin, M. Z.; Zhang, W.; Yang, L.; Liu, Z. L. Tetrahedron Lett. 2002, 43, 9687-9689.
- (a) Seeberger, P. H.; Danishefsky, S. J. Acc. Chem. Res. **1998**, 31, 685–695; (b) Lorsbach, B. A.; Kurth, M. J. Chem. Rev. **1999**, 99, 1549–1582; (c) Sammelson, R. E.; Kurth, M. J. Chem. Rev. **2001**, 101, 137–202.

- For selective examples, see: (a) Vitry, C.; Vasse, J. L.; Dupas, G.; Levacher, V.; Queguiner, G.; Bourguignon, J. *Tetrahedron* 2001, *57*, 3087–3098; (b) He, R.; Toy, P. H.; Lam, Y. Adv. Synth. Catal. 2008, 350, 54–60; (c) Che, J.; Lam, Y. L. Adv. Synth. Catal. 2010, 352, 1752–1758; (d) Alza, E.; Sayalero, S.; Kasaplar, P.; Almasi, D.; Pericas, M. A. Chem. Eur. J. 2011, *17*, 11585–11595.
- For selective examples, see: (a) Nakamura, K.; Fujii, M.; Oka, S.; Ohno, A. Bull. Chem. Soc. Jpn. **1987**, 60, 2423–2427; (b) Fujii, M. Bull. Chem. Soc. Jpn. **1988**, 61, 4029–4035; (c) Fujii, M.; Aida, T.; Yoshihara, M.; Ohno, A. Bull. Chem. Soc. Jpn. **1989**, 62, 3845–3847; (d) Li, J.; Cao, J. J.; Wei, J. F.; Shi, X. Y.; Zhang, L. H.; Feng, J. J.; Chen, Z. G. Eur. J. Org. Chem. **2011**, 229–233; (e) Chen, W.; Li, P. H.; Wang, L. Tetrahedron **2011**, 67, 318–325.
- Zhang, B. L.; Zhu, X. Q.; Lu, J. Y.; He, J.; Wang, P. J.; Cheng, J. P. J. Org. Chem. 2003, 68, 3295–3298.
- 9. Mei, L. R.; Zhu, X. Q.; Cheng, J. P. Chin. Sci. Bull. 2010, 55, 2824-2828.
- 10. Liu, J. H. Master Thesis, School of Chemistry. Nankai University, 2005.

- 11. Mackiewicz, N.; Delaire, J. A.; Rutherford, A. W.; Doris, E.; Mioskowski, C. *Chem. Eur. J.* **2009**, *15*, 3882–3888.
- 12. Xu, H. J.; Wan, X.; Shen, Y. Y.; Xu, S.; Feng, Y. S. Org. Lett. 2012, 14, 1210–1213.
- Feng, Y. S.; Ma, J. J.; Lin, X. Y.; Zhang, J. S.; Lv, P.; Xu, H. J.; Luo, L. B. Chin. Chem. Lett. 2012, 23, 1411–1414.
- For some previous studies on the conjugates of coenzymes with water-soluble polymers as enzyme models, please see: (a) Liu, L.; Breslow, R. J. Am. Chem. Soc. 2002, 124, 4978–4979; (b) Liu, L.; Rozenman, M.; Breslow, R. J. Am. Chem. Soc. 2002, 124, 12660–12661; (c) Liu, L.; Breslow, R. Bioorg. Med. Chem. 2004, 12, 3277–3287.
- 15. Zolfigol, M. A.; Safaiee, M. Synlett 2004, 5, 827-828.
- 16. Xu, H. J.; Liu, Y. C.; Fu, Y.; Wu, Y. D. Org. Lett. 2006, 8, 3449-3451.
- 17. After the reaction the catalyst was recovered by dialysis (see Supplementary data). The amount of reactants was recalculated by the amount of recycling catalyst. And the other reaction conditions are constant.