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Polysiloxane-Supported NAD(P)H Model 1-Benzyl-1,4-dihydronicotinamide: Synthesis and Application in the Reduction of Activated Olefins

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Abstract: A new polysiloxane-supported NAD(P)H model, 1-benzyl-1,4-dihydronicotinamide, was designed and synthesized, which can efficiently reduce many activated olefins under mild conditions. The most advantageous features of this new polysiloxane-supported reductant are (i) easy workup and separation of the reaction products and (ii) good potential for recycling use of the reductant, which makes this new polysiloxane-supported NAD(P)H model a promising alternative both in research laboratories and in industrial processes.

Nicotinamide adenine dinucleotide (NADH) and its phosphate derivative (NADPH) have long been known to act as coenzymes in biological redox reactions. It was established that in the reduced form of the coenzyme the active part is 1,4-dihydropyridine.[1] Thus, 1-benzyl-1,4-dihydronicotinamide (BNAH), Hantzsch 1,4-dihydropyridine (HEH), 10-methyl-9,10-dihydroacridine ($AcrH_2$), and many other 1,4-dihydropyridine derivatives are widely used as models to mimic the function of NAD(P)H in biological reductions of various unsaturated compounds.[2−6] Tremendous activities have been carried out to focus on the mechanistic details of these systems. To our knowledge, however, little attention has been paid to these models acting as reducing agents in organic synthesis except for a few cases where some chiral NAD(P)H models were used.[7] In fact, these NAD(P)H model compounds themselves generally possess excellent reducibility, so that they may be effectively applied in the reduction of many unsaturated substrates.[8]

As green chemistry has become a major concern to organic chemists in recent years,[9] solid or solid-supported catalysts have received much more attention, because they may offer several advantages in preparative procedures, e.g., simplifying workup and separation and recycling of the catalyst. These features may lead to economical automation and may effectively reduce pollution of hazardous compounds, advancing to an environmentally benign process.[10] In this connection, immobilizing NAD(P)H models not only provides a novel design for a new reductant, but may also lead to an efficient green methodology for organic synthesis. In a previous paper,[11] a polymer-bound NAD(P)H model was reported, which consisted of NAD(P)H model 1-benzyl-1,4-dihydronicotinamide and a copolymer of styrene and divinylbenzene (Merrifield-type resin). However, Merrifield resin is largely affected by solvents, i.e., swelling in an organic medium and contracting in an aqueous solvent, which evidently retards the reduction of the $NAD(P)^+$ model moiety inside the polymer in a basic aqueous medium in the preparation of the polymer-bound NAD(P)H model. SiO_2 is an inorganic support and is little affected by solvents. Recently, SiO_2 has received much attention in catalyst immobilization and solid-phase synthesis,[12] and a few papers concerning the immobilization of a NAD(P)H model on silica have appeared, which was performed by grafting silica onto the nitrogen atom at the 1-position on the pyridine ring.[13] As well-known, the

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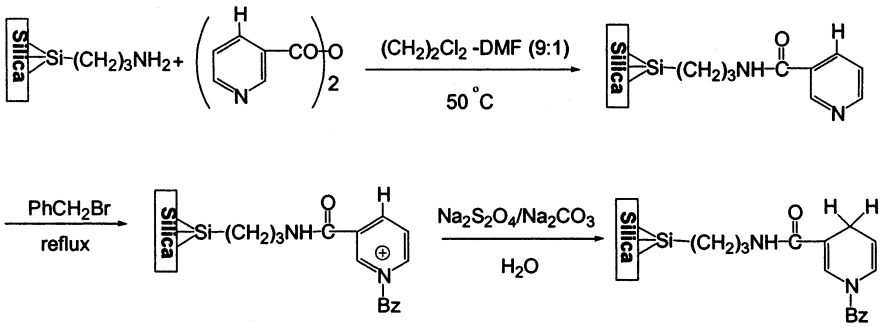
SCHEME 1



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reactivity of NAD(P)H models is strongly dependent on the size of the substituent at the 1-position on the pyridine ring; silica grafted onto the nitrogen atom at the 1-position, of course, must make the reactivity of NAD(P)H models quite low. In addition, polysiloxane has been confirmed to be a much better inorganic support than silica and has a higher content of functional groups,[14] which inspired us to graft polysiloxane onto the nitrogen atom in the $CONH_2$ group of the nicotinamide. We report here the synthesis of polysiloxane-immobilized 1-benzyl-1,4-dihydronicotinamide (polysiloxane−BNAH, **1**) and its successful application in the reduction of some activated olefins.

The synthetic route of polysiloxane−BNAH is shown in Scheme 1. Aminopolysiloxane[14] was treated with nicotinic anhydride to give the corresponding polysiloxane-grafted nicotinamide, which was then refluxed with benzyl bromide in acetonitrile to give polysiloxane-grafted 1-benzylnicotinamide cation. The formed intermediate cation was reduced by sodium dithionite in basic aqueous solvent to offer polysiloxane−BNAH, with 0.75 mmol of 1,4-dihydropyridine/g of polysiloxane−BNAH.[15]

To find the applicability of this new polysiloxane-supported NAD(P)H model as a reductant in organic synthesis, many activated olefins (**2**) and some allylic and benzylic bromides (**6** and **7**) were examined. When the olefins **2a**−**2n** were treated with **1** in dry acetonitrile at room temperature, the reaction results showed that the double bond in **2** was efficiently reduced. If the substrate **6** was treated with **1** in dry acetonitrile at room temperature, cyclopropane derivative **8** and its open-chain compound **9** as the reduction products were obtained, but if the substrate **7** was used instead of **6** to react with **1**, only indan derivative **9** was obtained. The detailed results are summarized in Tables 1 and 2.

As shown in Table 1, the new polysiloxane-supported NAD(P)H model can effectively reduce olefins which are activated by electron-withdrawing groups such as CN and CO_2Et. When the olefin is benzylidenemalononitrile and ethyl α-cyanocinnamate and their derivatives **2a**−**2n**, the reactions give the corresponding double-bond-reduced products **4** in excellent yield, suggesting a potential synthetic application of the new reductant for activated olefins under mild conditions. According to the reaction time and product yields, it is clear that benzylidenemalononitrile and its derivatives are more efficient than the corresponding ethyl α-cyanocinnamate and its derivatives in the reductions, which indicates the developing negative charge on the active center of the substrate during the reduction processes, since the power of CN to attract electrons (Hammett substituent parameter $\sigma = 0.66$)[16] is larger than that of CO_2Et ($\sigma = 0.45$),[16] which makes the kinetic barrier to attack the double bond easier to overcome. For the same reason, it is quite understandable that no reaction was observed with olefin **2o**, because NMe_2 is a very strong electron-donating group ($\sigma = -0.83$).[16] A tentative reaction mechanism of **2** with **1** may be proposed as shown in Scheme 2: a hydride departed from the dihydropyridines first attached to the β-carbon of **2** to form a carbanion intermediate, which then attracted a proton to form the final reduction product **4**. It is worth noting that when 9-fluorenylidenemalononitrile and ethyl α-cyano-9-fluorenylideneacetate (**2p** and **2q**) are used as substrates, two products are formed; one is the double-bond-reduced products **4** and the other is hydrolytic decomposition product ketones **5**. From the yield ratio of **4** to **5**, it is clear that reducing the electron-withdrawing power of X favors the generation of **5**. Following the same trend, it should be expected that **4** should be further disfavored if X is a hydrogen atom or one R group is an electron-donating group. Indeed, this is exactly what we observed with olefins **2r**−**2w**. These reactions went very slowly, and the product was only ketones **5**. To probe the formation route of **5**, free BNAH was used instead of **1** to react with **2r**−**2w**; no **5** was observed for 3 days, which ruled out the possibility that **5** formed from the direct reaction of olefin with **1**. But if the free polysiloxane was used instead of **1** to react with olefin **2s**, **5s** was obtained also, which indicates that **5** must come from a slow reaction of olefin with the trace of water contained in polysiloxane.[17] This hydrolytic reaction, of course, should be

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(15) The content of the 1,4-dihydropyridine units was estimated by the reaction with *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine radical cation perchlorate in anhydrous acetonitrile. 1,4-Dihydropyridine can be rapidly oxidized by *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine radical cation perchlorate, so that the content of the 1,4-dihydropyridine can be determined by the decrease in the absorption at λ = 564 nm.

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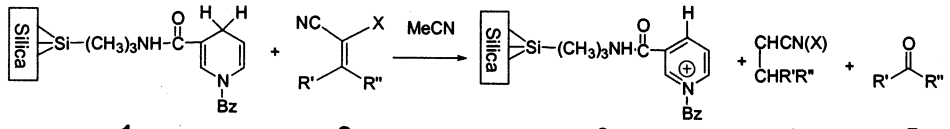
TABLE 1. Reactions of 1 with Activated Olefins 2 in Dry Acetonitrile[a]

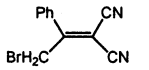
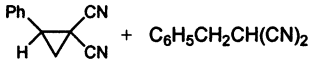
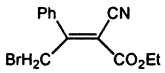
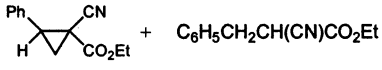
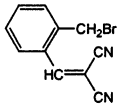
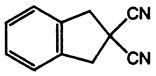
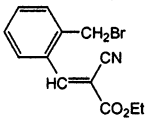
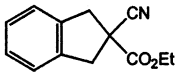


1 **2** **3** **4** **5**

	activated olefins						
compd	R′	R″	X	*T* (°C)	time (h)	products	yield[b] (%)
2a	Ph	H	CN	rt	1	**4a**	92
2b	*m*-BrPh	H	CN	rt	1	**4b**	95
2c	*m*-FPh	H	CN	rt	1	**4c**	95
2d	*m*-ClPh	H	CN	rt	1	**4d**	93
2e	*p*-CF_3Ph	H	CN	rt	1	**4e**	96
2f	*p*-CH_3Ph	H	CN	rt	3	**4f**	93
2g	*p*-OCH_3Ph	H	CN	rt	3	**4g**	65
2h	Ph	H	CO_2Et	rt	5	**4h**	80
2i	*p*-CF_3Ph	H	CO_2Et	rt	5	**4i**	90
2j	*m*-FPh	H	CO_2Et	rt	5	**4j**	95
2k	*p*-CH_3Ph	H	CO_2Et	rt	5	**4k**	90
2l	*p*-ClPh	H	CO_2Et	rt	3	**4l**	95
2m	*m*-BrPh	H	CO_2Et	rt	5	**4m**	93
2n	*p*-OCH_3Ph	H	CO_2Et	rt	4	**4n**	90
2o	*p*-$N(CH_3)_2$Ph	H	CO_2Et	rt	48	no reaction	
2p	9-fluorenylidene		CN	rt	12	**4p** (65) + **5p** (5)[c]	
2q	9-fluorenylidene		CO_2Et	rt	12	**4q** (40) + **5q** (19)[c]	
2r	9-fluorenylidene		H	rt	50	**5r**	17
2s	Ph	CH_3	CN	rt	24	**5s**	17
2t	Ph	c-Pr	CN	rt	24	**5t**	15
2u	Ph	CH_3	CO_2Et	rt	24	**5u**	11
2v	CH_3	Ph	CO_2Et	rt	24	**5v**	14
2w	Ph	CH_3	$CONH_2$	rt	24	**5w**	15

[a] All reactions were carried out as described in the Experimental Section; olefin:**1** = 1:1.5 (mol/mol). [b] Yields of isolated products after chromatographic purification. [c] Determined by capillary GC analysis of the crude reaction mixture after filtration.

TABLE 2. Cyclizations of Some Allylic and Benzylic Bromides by 1 in CH_3CN under an Argon Atmosphere[a]

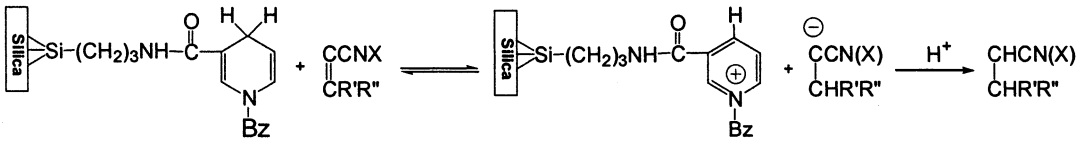
Substrates (No.)		ratio[b]	T(℃)	time (hrs)	products (yield %)[c]
	**(6a)**	1.5 : 1	rt	1.5	 **8a (28%)** **4a (72%)**
	**(6b)**	1.5 : 1	rt	2	 **8b (34%)** **4h (66%)**
	**(7a)**	1.5 : 1	rt	2	 **9a (87%)**
	**(7b)**	1.5 : 1	rt	3	 **9b (87%)**

[a] All reactions were carried out as described in the Experimental Section. [b] Molar ratio of **1** to the substrate. [c] Yields of isolated products.

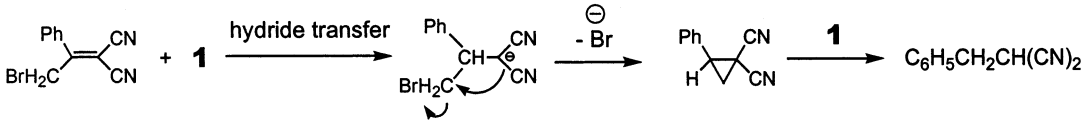
largely depressed when a more activated olefin is used, because the reduction reaction runs much faster.

In Table 2, it is interesting to find that when the substrates are 2-bromo-1-phenylethylidenemalononitrile (**6a**) and its analogue **6b**, the reduction products are cyclopropane derivatives **8a** and **8b** along with their open-chain compounds **4a** and **4h**, and the open-chain compounds are major products (see Table 2), but if the substrate is *o*-bromomethylbenzylidenemalononitrile (**7a**) and its analogue **7b**, only indan structure compounds **9** without open-chain compounds are obtained. Concerning the cyclization mechanisms of the substrates **6** and **7**, it is reasonable to propose that the reactions take place via a hydride-transfer mechanism, similar to the proposal in our previous paper.[8] Thus, a hydride ion from **1** added to the benzyl position of the substrates and the resulting

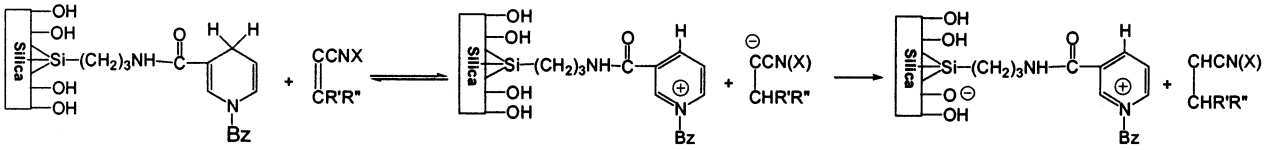
SCHEME 2



SCHEME 3



SCHEME 4



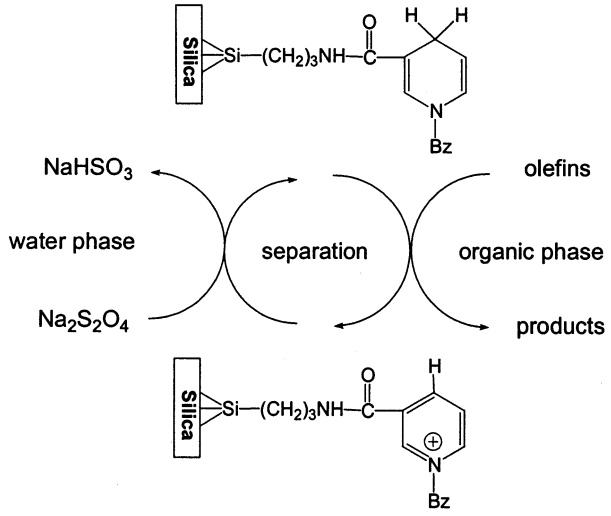
carbanions undergo (i) in the cases of **6a** and **6b**, intramolecular displacement of the *β*-bromomethyl group to produce cyclopropane derivatives **8a** and **8b**, which then are further reduced by **1** to become the final open-chain product **9** as shown in Scheme 3 and (ii) in the cases of **7a** and **7b**, intramolecular nucleophilic substitution of the *o*-bromomethyl group to produce indan derivatives **9** after initial hydride transfer. It is worth noting here that since the stability of five-membered ring compounds **9** is larger that that of three-membered ring compounds **8**, the indan derivatives **9** cannot be further reduced by **1** to become the open-chain product.

The solvent effect on the reactions was also examined. As well-known, for the reactions using free NAD(P)H models such as BNAH, a polar solvent such as acetonitrile is quite suitable and a small amount of protic solvent such as methanol is also required. The reason is that proton can neutralize the carbanion intermediate formed from the initial formal hydride transfer to make the reaction go to the right and to prevent the reverse reaction to the left (Scheme 2). But for the reactions with polysiloxane-grafted NAD(P)H model **1**, a change of the solvent system to, e.g., CH_2Cl_2, 1,4-dioxane, THF, benzene, etc. did not cause a remarkable difference in the product yields. It is worth noting that, unlike the reactions with regular models, in the reactions with polysiloxane−BNAH, no protic medium was needed. The main reason could be that the free silanol groups on silica can offer protons to neutralize the formed carbanion and thus drive the reduction to completion (Scheme 4).[17]

The most appealing advantage of polysiloxane−BNAH as a reductant is its recycling use. To test this point, the polysiloxane−BNA^+ formed from the reaction of polysiloxane−BNAH with olefins **2** was reduced with sodium dithionite in a basic medium, and then was treated with the substrate again. It showed no obvious decrease in reactivity after the reductant was reused three times. The recycling operation of polysiloxane−BNAH is demonstrated in Scheme 5.

In summary, we present here the first covalent heterogenization of the NAD(P)H model on polysiloxane,

SCHEME 5. Cyclic Pathway for the Sodium Dithionite-Mediated Reduction of Olefins with Polysiloxane−BNAH



which retains the good reducing ability of NAD(P)H model compounds and also possesses several advantages of inorganic solid-phase synthesis so that it can be effectively used to reduce many activated olefins. The easy workup and separation of the products and the good potential for recycling use of the reagent make this new reductant a promising alternative both in research laboratories and in industrial processes.

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Supporting Information Available: Experimental details for the preparation of Polysiloxane-BNAH and characterization data of the representative products. This material is available free of charge via the Internet at http://pubs.acs.org.

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