

Solvent Effect on the Reversibility of Base Catalyzed Henry Reactions

– Triton B Catalyzed Nitro Aldol Reactions in Alcohol –

Fumiyasu Ono^{*1}, Hiroe Soejima^{*1}, Junji Tanaka^{*2}, and Shuji Kanemasa^{*2†}

[†]E-mail of corresponding author: kanemasa@cm.kyushu-u.ac.jp

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The amine catalyzed nitro aldol reactions between nitromethane and aldehydes are found to be reversible in an alcohol solvent on the basis of the reaction monitoring by ¹H NMR spectroscopy. The reaction in alcohols is particularly rapid to complete the equilibrium in a short period of time at room temperature, producing nitro aldol product in high yields. Triton B is especially effective as catalyst in the nitro aldol reactions of nitromethane in methanol. Only a small catalytic loading of triton B as small as 1 mol% is enough to finish the reaction. Aromatic, aliphatic, and α,β -unsaturated aldehydes as well as aldehyde hydrates and aqueous aldehydes are successfully employed

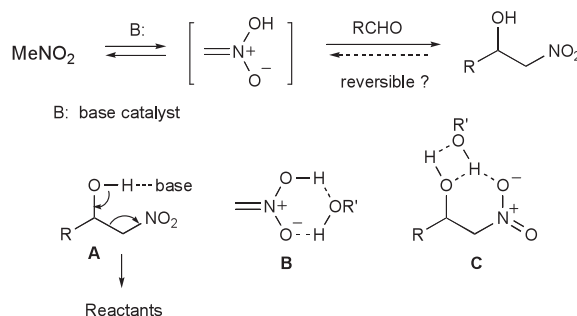
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1. Introduction

Nitro aldol reactions known as Henry reactions provide a useful access for the carbon-carbon bond formation. The resulting β -nitro alcohols are easily converted to a variety of useful multi-functionalized synthetic intermediates such as nitroalkenes, α -nitro ketones, and β -amino alcohols.¹⁻³ The Henry reaction is accompanied by side reactions since these reactions are often reversible depending upon the nature of substrates and products as well as the reaction conditions. However, direct observation of the reversibility of base catalyzed Henry reactions remains still unclear.

The base catalyzed Henry reaction starts with the deprotonation of nitroalkanes with a base at α -position to generate the corresponding resonance stabilized carbanion. An aldol reaction takes place between the nucleophile and carbonyl compounds to form β -nitro alkoxides. The β -nitro alkoxides are protonated to give β -nitro alcohols. Reversibility of this sequence would be minimized if one can stabilize nitro aldol products rather than the reactants as shown in Scheme 1. On these aspects, we started a study to control the reversibility of base catalyzed Henry reactions by use of a variety of solvents, with an expectation that the right selection of reaction solvent as well as reaction conditions should be a key to success. It may be apparent that the retro reaction is initiated by deprotonation of nitro aldols as shown with A. Use of protic solvent such as alcohol would accelerate the forward reaction via stabilization of the nitro enol

intermediates and product, as shown with B and C, respectively.



Scheme 1. The way for controlling base catalyzed nitro aldol reactions.

In this communication, we demonstrate the base catalyzed Henry reactions of nitromethane with aldehydes in a variety of solvents. The relative reaction rates are observed in several deuterated solvents showing that methanol causes the highest rate acceleration among the solvents tested. In addition, the equilibrium position was much favored in methanol for the nitro aldols. Aqueous benzyltriethylammonium hydroxide (triton B) works as especially excellent base catalyst for the Henry reactions in methanol. Only a small catalytic loading of triton B as small as 1 mol% is enough to finish the reaction in a short period of time.⁸ Aromatic, aliphatic, and unsaturated aldehydes as well as hydrated aldehydes were successfully applied.

*1 Department of Molecular and Material Sciences

*2 Institute for Materials Chemistry and Engineering, CREST of JST (Japan Science and Technology Agency)

2. Results and Discussion

The reaction between nitromethane (5 equiv) and *p*-methylbenzaldehyde was monitored by ^1H NMR analysis at room temperature in an NMR sample tube in some deuterated solvents such as methanol- d_4 (CD_3OD), tetrahydrofuran- d_8 (THF- d_8), and dichloromethane- d_2 (CD_2Cl_2) in the presence of a catalytic amount of amine and 1,4-dimethoxybenzene as internal reference. Some of the reaction profiles observed in each solvent are given in Fig. 1. When 2,2,6,6-tetramethylpiperidine (TMP) was used as base catalyst (5 mol%), the reaction in methanol- d_4 (0.5 M) was found to complete in 3 h to give a mixture of 2-nitro-1-(*p*-methylphenyl)ethanol and *p*-methylbenzaldehyde in 86/14% yields, respectively, based on the relative integrations to internal reference (reaction 'a'). Although the reaction monitoring was further continued to 120 h, the relative product ratio did not change any more, indicating that the reaction is in a steady equilibration.

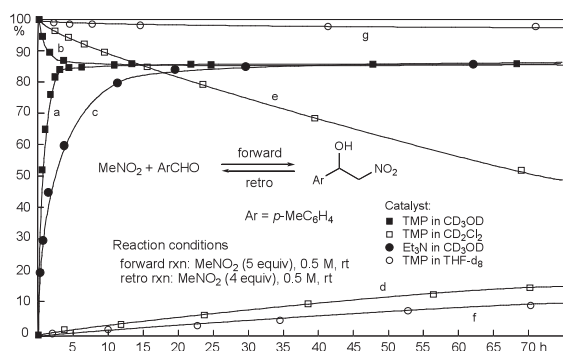


Fig.1 Solvent effect for the reversible Henry reactions between nitromethane and *p*-methylbenzaldehyde catalyzed by amines (5 mol%, rt).

The crude nitro aldol was separated and purified through silica gel column chromatography, and this pure sample obtained was employed to examine the reverse reaction. This sample was treated with an excess of nitromethane (4 equiv) and 5 mol% of TMP catalyst in methanol- d_4 (0.5 M) at room temperature. The reaction was again continued to monitor and we observed the occurrence of retro reaction giving an 86/14 mixture of nitro aldol and *p*-methylbenzaldehyde in a period of 3 h (reaction 'b'). Thus, the nitro aldol actually underwent the retro reaction 'b' under the base catalyzed conditions to give the same product ratio (86/14) as the forward reaction 'a'. This indicates that the TMP catalyzed nitro aldol reaction between nitromethane and *p*-methylbenzaldehyde rapidly reaches to equilibration in methanol solution. Catalysis with triethylamine (reaction 'c') was a little slower than that of TMP (reaction 'b'). The reactions 'a, b, c' came to the same composition of products with the nitro aldol/aldehyde ratio of 86/14. This product ratio, cor-

responding to the yield of nitro aldol, is not dependent of the catalyst.

On the other hand, the Henry reactions of nitromethane and *p*-methylbenzaldehyde in other solvents such as dichloromethane- d_2 and tetrahydrofuran- d_8 were very much slow, compared to the reaction in methanol- d_4 (reactions 'a' vs 'd' and 'a' vs 'f'); the corresponding nitro aldol product was formed only in 12% yield in dichloromethane- d_2 (reaction 'd') and 8% in tetrahydrofuran- d_8 (reaction 'f') after 60 h at room temperature. Thus, alcohol such as methanol was the best choice as reaction solvent for the amine catalyzed Henry reactions.

Although the reverse reaction in methanol- d_4 (reaction 'b') quickly came to equilibrium in 3 h, as mentioned above, the reverse reaction in tetrahydrofuran- d_8 was very much slow (reaction 'g'); only less than 3% of the nitro aldol underwent the retro reaction even after 120 h at room temperature. In contrast, the retro reaction in dichloromethane- d_2 was relatively fast to liberate the aldehyde in 65% after 110 h (reaction 'e'). Apparently, the product ratios in equilibrium are highly dependent on the reaction solvents. The Henry reactions in tetrahydrofuran- d_8 and dichloromethane- d_2 were so slow, both for the forward and reverse reactions, that these could not reach equilibration in the period of our experiments. However, we can learn from the reaction monitoring results shown in Fig. 1 that these two solvents show different nitro aldol/aldehyde compositions at the equilibrium: The forward reaction is faster than the reverse reaction in tetrahydrofuran, but the reverse reaction is faster than the forward reaction in dichloromethane.

Although the big difference of solvent effects for the equilibrium composition between tetrahydrofuran and dichloromethane remains unclear, the high rate enhancement and establishment of equilibrium in favor of nitro aldol in methanol may be well explained by the effective stabilization of the nitro enol intermediate and nitro aldol product by methanol. Hydrogen bonding may be playing an important factor for high stabilization, as shown with complexes **B** and **C** in Scheme 1.

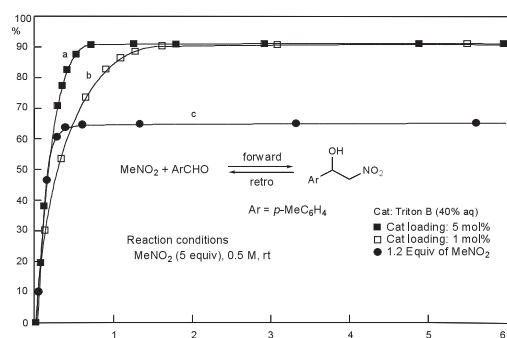


Fig.2 Triton B catalyzed nitro aldol reactions between nitromethane and *p*-tolualdehyde in methanol at rt.

If a strong base catalyst which can be utilized effectively in methanol is available, we will be able to attain the highly effective Henry reactions catalyzed with a small amount of catalyst. The catalyst we chose was benzyltriethylammonium hydroxide, known as triton B, which is commercially available as 40 wt% of aqueous solution. Triton B would be an ideal base catalyst in methanol solvent, since the aqueous solution is fully soluble in methanol. However, to the best of our knowledge, no reactions have been reported for the triton B catalyzed nitro aldol reactions in alcohol media.

As expected, the reaction between nitromethane (5 equiv) and *p*-methylbenzaldehyde was successfully catalyzed with a catalytic amount of triton B (5 mol%) in methanol- d_4 (Fig. 2, reaction 'a'). The reaction was finished within 30 min at room temperature to give the nitro aldol product in 91% yield. Even when the catalytic loading was reduced to 1 mol%, the reaction reached the maximum equilibrium mixture including 91% yield of the nitro aldol in 1.5 h (reaction 'b'). When nitromethane was reduced to an approximately equimolar amount (1.2 equiv), yield of the nitro aldol was decreased to 65% yield (reaction 'c'), again confirming reversibility of the reaction. Thus, the Henry reactions between nitromethane and *p*-methylbenzaldehyde can rapidly reach equilibration in methanol in a short period of time with a small catalytic loading of triton B. Since yield of the nitro aldols depends upon the amounts of substrates used, either nitromethane or *p*-methylbenzaldehyde has to be used in excess. Nitromethane is the reagent which should be used in excess in this reaction, since it is readily removable through evaporation after the completion of reaction. Anyhow, it is clear also that the triton B catalyzed reaction is under rapid equilibration.

With the above success, we then applied the nitro aldol methodology using nitro alkanes to a variety of combinations of donor and acceptor molecules under the catalysis of triton B in methanol. The results observed are summarized in Table 1.

Entry	Nitro alkane	Carbonyl compound	cat/mol%	Time/h	Products	Yield/%
1	MeNO ₂ 1	<i>p</i> -MeC ₆ H ₄ CHO	5a	1	6a	91
2		<i>p</i> -NO ₂ C ₆ H ₄ CHO	5b	1	6b	quant
3		2-HOC ₆ H ₄ CHO	5c	5	6c	76
4		2-PyCHO	5d	1	6d	quant
5		2-ThienylCHO	5e	5	6e	79
6		EtCHO	5f	5	6f	79
7		PhCH ₂ CHO	5g	5	6g	89
8		PhCH ₂ CH ₂ CHO	5h	1	6h	91
9		(<i>E</i>)-PhCH=CHCHO	5i	5	6i	44
10		HCHO aq	5j	5	6j	38
11		CCl ₃ CH(OH) ₂	5k	5	6k	84
12 ^b		MeCOMe	5l	5	6l	nr
13	EtNO ₂ 2	<i>p</i> -NO ₂ C ₆ H ₄ CHO	5b	1	7	quant
14	<i>n</i> -PrNO ₂ 3	<i>p</i> -NO ₂ C ₆ H ₄ CHO	5b	1	8	quant
15	<i>i</i> -PrNO ₂ 4	<i>p</i> -MeC ₆ H ₄ CHO	5a	5	9	41

^aDonor (5 equiv), Triton B (40% aqueous), 0.5 M in MeOH, rt. ^bCH₃NO₂ (1 equiv), MeCOMe (11 equiv), 0.8 M

Table.1 Triton B catalyzed Henry reaction in methanol at rt.

Reactions of nitromethane (**1**) with reactive aldehydes, such as *p*-methylbenzaldehyde (**5a**), *p*-nitrobenzaldehyde (**5b**), 2-pyridinecarboxaldehyde (**5d**), and 3-phenylpropanal (**5h**) smoothly proceeded with 5-fold excess amounts of nitromethane (**1**) in the presence of 1 mol% of triton B in methanol (0.5 M) in 1 h at room temperature to produce the corresponding nitro aldol adducts **6a**, **b**, **d**, **h** in nearly quantitative yields (entries 1, 2, 4, 8). For less reactive aromatic aldehydes such as salicylaldehyde (**5c**) and 2-thiophenecarboxaldehyde (**5e**), 5 mol% of the catalyst was needed (entry 3, 5), and propanal (**5f**) as simple aliphatic aldehyde was also successfully catalyzed with 5 mol% of triton B.

Both phenylacetaldehyde (**5g**) as highly enolizable aldehyde and cinnamaldehyde (**5i**) as α,β -unsaturated aldehyde showed comparable reactivities (entries 7, 9). It was our delight to learn that no other products were even detected through either self aldol condensation of **5g** or through Michael addition reaction of **1** to **5i**, normal nitro aldol products **6g**, **i** being the only isolated products.

Aqueous formaldehyde (**5j**, 37 wt % solution in water) and the hydrate of trichloroacetaldehyde (**5k**, chloral hydrate) were also successfully utilized in the Henry reactions of **1** in the presence of 5 mol% of Triton B in methanol to give **6j**, **k**, respectively, in moderate yields (entries 10, 11). However, the reaction of **1** (1 equiv) with acetone (**5l**) did not take place at all even if **5l** was used in a large excess (11 equiv) (entry 12). Primary nitroalkanes such as nitroethane (**2**) and nitropropane (**3**) smoothly reacted with aldehyde **5b**, under the catalysis of 1 mol% of triton B in 1 h at room temperature, to give diastereomer mixtures of the corresponding nitro aldols **7** and **8** in quantitative yields (entries 13, 14).⁹ Even a sterically hindered 2-nitropropane (**4**) as secondary nitro alkane reacted with aldehyde **5a** to give nitro aldol **9** having a quaternary carbon, albeit in a low yield (entry 15).

In conclusion, on the basis of the reaction monitoring by ¹H NMR spectroscopy, the amine catalyzed nitro aldol reaction between nitromethane and *p*-methylbenzaldehyde is found to proceed reversibly. The reaction in alcohols is particularly rapid to complete the equilibrium in a short period of time at room temperature, producing nitro aldol product in high yields. The forward reactions in both dichloromethane and THF are relatively very slow. Although the retro reaction is moderate in dichloromethane, that in tetrahydrofuran- d_8 is almost frozen. Triton B is the especially effective catalyst in the nitro aldol reactions of nitromethane in methanol. Only a small catalytic loading of triton B as small as 1 mol% is enough to finish the reactions for aromatic, aliphatic, α,β -unsaturated aldehydes as well as hydrate aldehydes and aqueous aldehydes.

Acknowledgments

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