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Graphical Abstract

“On water” direct vinylogous Henry (nitroaldol) reactions of 3,5-dimethyl-4-nitroisoxazole with aldehydes and trifluoromethyl ketones

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“On water” direct vinylogous Henry (nitroaldol) reactions of 3,5-dimethyl-4-nitroisoxazole with aldehydes and trifluoromethyl ketones

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ABSTRACT

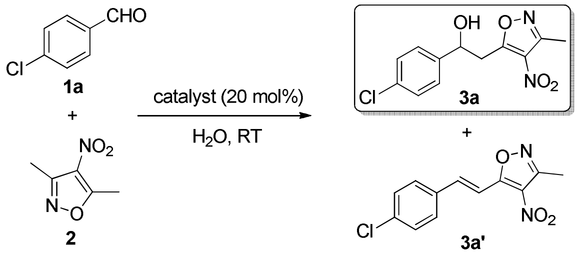
An efficient “on water”-promoted direct catalytic vinylogous addition of 3,5-dimethyl-4-nitroisoxazole to aldehydes and trifluoromethyl ketones was described, giving Henry (nitroaldol) adducts in excellent yields. The trifluoromethyl tertiary alcohol product could be transformed to the corresponding styrene derivative, which was demonstrated as a new type of Michael acceptor in the vinylogous 1,6-Michael addition with nitromethane.

The use of water as solvent for organic synthesis is regarded as an important subject in green chemistry, because water is cheap, nontoxic, nonflammable, and the most abundant liquid on our planet.[1] In addition, water has unique physical and chemical properties, which allows us to realize reactivities that cannot be achieved in conventional organic solvents. In the early 1980s, Breslow and coworkers uncovered rate enhancement of Diels-Alder reactions using water as the solvent.[2] About 25 years later, Sharpless and co-workers introduced the concept of “on water” to explain the unusual reaction rate acceleration when the organic reactants were insoluble in the aqueous phase.[3] Since these two seminal findings, many organic reactions have been tested under on water conditions to improve synthetic efficiency.[4] However, developing new type of reaction in water is still highly desirable.

With the exploitation of the vinylogy concept[5], the vinylogous-type reactions have emerged as effective strategies for remote functionalizations and have been intensively studied in recent years.[6] However, so far, only a few examples of the vinylogous-type reactions using pre-enolized reagents on water have been reported.[7] In the course of our studies on vinylogous-type reactions[8], we recently reported an “on water” promoted direct vinylogous addition of 3,5-dialkyl-4-nitroisoxazoles to isatins.[9] Herein, we disclose an efficient vinylogous Henry (nitroaldol) reaction between 3,5-dimethyl-4-nitroisoxazole and aldehydes[10] as well as trifluoromethyl ketones using water as the solvent.

Using *p*-chlorobenzaldehyde (**1a**) and 3,5-dimethyl-4-nitroisoxazole (**2**) as the model substrates and water as the solvent, we initially screened NEt_3 as the base catalyst to effect the desired vinylogous Henry (nitroaldol) reaction between **1a** and **2**. As shown by the data in Table 1 (entry 1), when the reaction was carried out with 20 mol% of NEt_3 at room temperature for 15 h, the desired vinylogous adduct **3a** was obtained in high yield (92 %), together with 6% of dehydration product **3a′**. Some additional organic bases were then screened, and the obtained results are summarized in Table 1. Significant improvement in reaction efficiency was observed for DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene), but the selectivity is rather poor. DMAP (4-dimethylaminopyridine), DABCO (1,4-Diazabicyclo[2.2.2]octane), QD (qunidine) and diethylamine were not suitable for such a reaction in term of both reaction efficiency and selectivity. Inorganic bases such as NaOH and K_2CO_3 can also catalyze the reaction, albeit in slightly lower efficiency (entries 9 and 10).

Table 1 Screening of catalyst for the vinylogous addition of **2** to **1a**[a]



Entry	Catalyst	T (h)	**3a**/**3a′**Yield[b] (%)
1	triethylamine	15	92/6
2	DBU	3	50/32
3	DMAP	36	57/30
4	DABCO	48	36/19
5	QD	48	31/37

6	diethylamine	36	85/11
7	NaOH	48	86/nd
8	K_2CO_3	48	82/nd

[a] All of the reactions were performed with 0.22 mmol of **1a**, 0.2 mmol of **2** and 0.04 mmol of catalyst in 1 mL H_2O.

[b] Isolated yield.

Subsequently, we investigated the effect of solvent on the reaction between **1a** and **2** using NEt_3 as the catalyst (Table 2). Poor conversions were observed using polar aprotic solvents DMSO and DMF (entries 1 and 2), whereas no reaction took place in Et_2O, Toluene, DCM, MeCN and THF (entries 3-7). The use of MeOH afforded only a small amount of **3a** (entry 8). It is noteworthy that both the reaction efficiency and the selectivity rose dramatically with the increase of proportion of water in the co-solvent of H_2O–MeOH, despite the fact that the reaction system became heterogeneous (entries 9 and 10). When pure water was used as the solvent, the reaction proceeded effectively to afford the desired product in excellent yield (up to 92%) (entry 11). Lowering down the reaction temperature to 15 ^oC will reduce the yield of the dehydration product, and no obvious effect on the reaction rate was observed.

Table 2 Solvent effect on the NEt_3 catalyzed addition of **2** to **1a**[a]

Entry	Solvent	T (h)	**3a**/**3a′**Yield[b] (%)
1	DMSO	24	7/-
2	DMF	24	3/-
3	Et_2O	24	NR[c]
4	Toluene	24	NR
5	DCM	24	NR
6	MeCN	24	NR
7	THF	24	NR
8	CH_3OH	24	30/-
9	H_2O-CH_3OH (1:3)	24	48 /43
10	H_2O-CH_3OH (3:1)	15	85/8
11	H_2O	15	92/6
12[d]	H_2O	15	96/-

[a] Unless otherwise noted, the reaction was performed with 0.22 mmol of **1a**, 0.2 mmol of **2** and 0.04 mmol of NEt_3 in 1 mL solvent at RT.

[b] Isolated yield.

[c] No reaction.

[d] The reaction was carried out at 15 ^oC.

An oil–water interface between reactants and water was assumed to explain the high efficiency of this process[9]. As illustrated in Figure 1, through the interactions with hydrogen-bond networks at the phase boundary, the nitro-group of the nucleophile and the carbonyl group of the electrophile might be organized at the periphery of the oil droplet, while the hydrophobic part is positioned within the hydrophobic interior. As a result, the free hydroxyl groups at the interface effectively activated the reactants and stabilized the transition state through hydrogen-bond. Moreover, the dehydration process could be suppressed when water was used as the sole solvent.

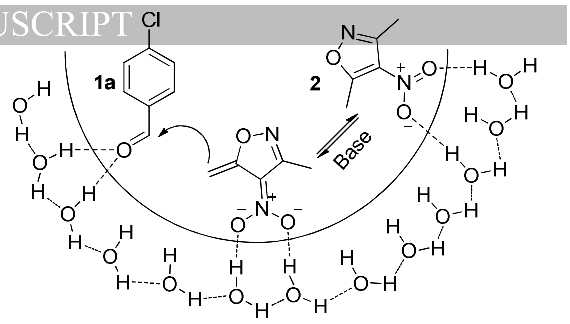
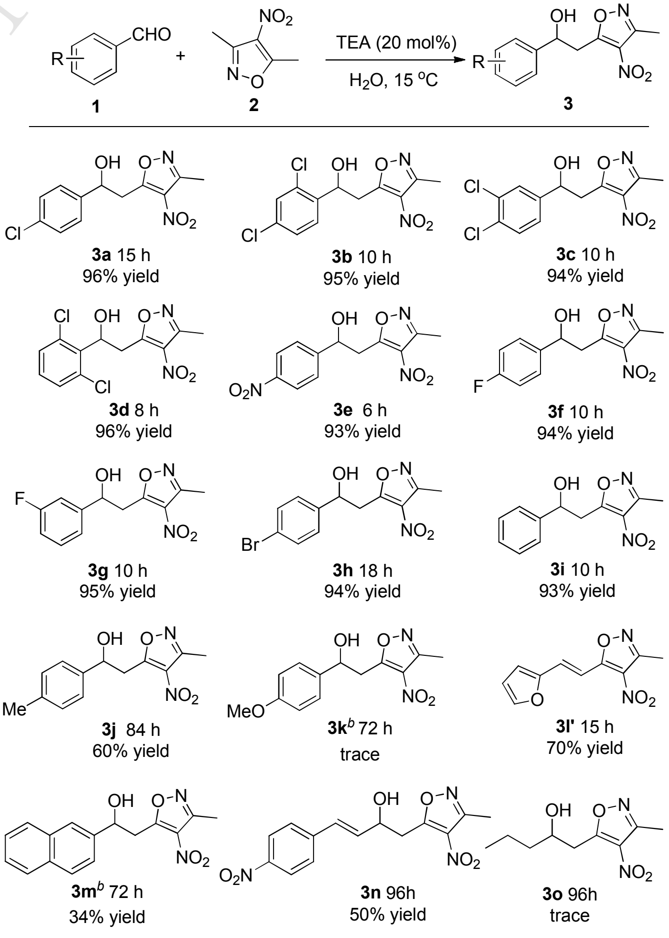


Figure 1 Proposed transition state.

These observations prompted us to study the scope and limitation of the direct vinylogous Henry reaction on a variety of aldehydes, using water as the solvent at 15 ^oC. The results are presented in Table 3. This "on water" vinylogous Henry reaction is compatible with a series of electon-deficient aromatic aldehydes, afforting the desired products **3a-3i** in excellent yields (93-97%). Both *p*-methyl benzaldehyde and 2-naphthaldehyde displayed low activity, giving the addition products **3j** and **3m** in moderate yields. No desired product was obtained for *p*-methoxybenzaldehyde bearing a stronger electron donating group. Heteroaromatic aldehydes such as 2-furaldehyde gave exclusively the undesired dehydration product **3l′** in moderate yield (70%). To our delight, α,β-unsaturated aldehyde (4-nitrocinnamaldehyde as an example) was also applicable, affording the 1,2 addition product **3n** in 50% yield. Aliphatic aldehyde[11] (*n*-butanal as an example) was not suitable in such reaction, gave no desired vinylogous product, presumably owing to its water solubility, which may not suitable for the "on water" reaction system.

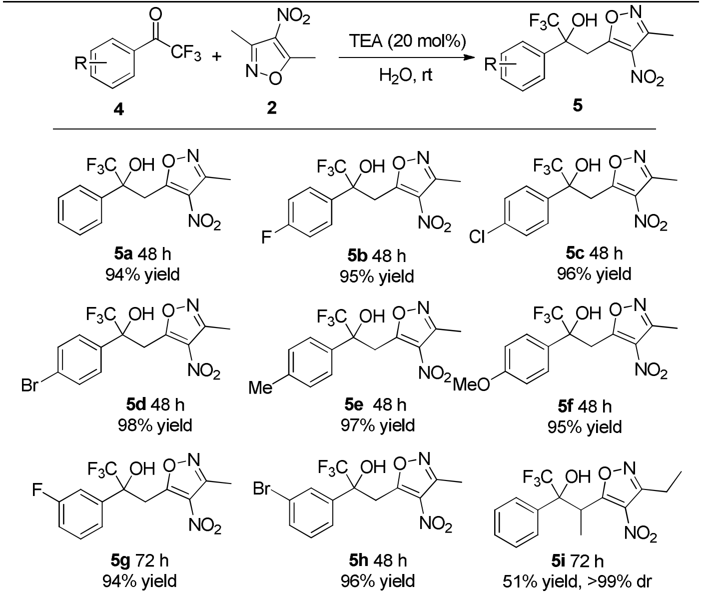
Table 3 Direct vinylogous Henry reactions of 3,5-dimethyl-4-nitroisoxazole with aromatic aldehydes[a]



[a] Unless otherwise noted, the reaction was performed with 0.22 mmol of **1**, 0.2 mmol of **2** and 20 mol% of NEt_3 in 1 mL water. The yield refers to the isolated yield.

[b] 30 mol% of the catalyst was used.

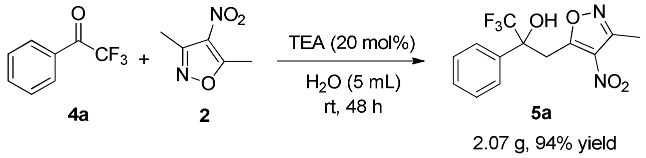
Table 4 Direct vinylogous Henry reactions of 3,5-dimethyl-4-nitroisoxazole with trifluoroacetophenone [a]



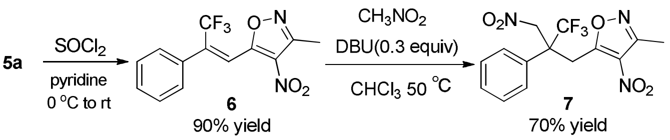
[a] Unless otherwise noted, the reaction was performed with 0.22 mmol of **4**, 0.2 mmol of **2** and 20 mol% of NEt_3 in 1 mL water. The yield refers to the isolated yield.

The synthetic flexibility of this "on water" reaction using 3,5-dimethyl-4-nitroisoxazole (**2**) was also expanded to various trifluoroacetophenone (**4**). Under the similar condition as mentioned in table 3, the desired vinylogous products **5** with a unique CF_3-bearing tertiary center were obtained in good to excellent yields. The electronic nature and the position of the substituents attached to the phenyl ring have no obvious impact on the efficiencies of the processes (Table 4). 3,5-diethyl-4-nitroisoxazole was also applicable in such reaction, affording the corresponding vinylogous Henry adduct **5i** in excellent diastereoselectivity (>99%), albeit with moderate yield (51%).

The potential of the "on water" catalytic protocol was further elaborated by performing a gram-scale synthesis of **5a**. Accordingly, treatment of 7.7 mmol of **4a** with 7.0 mmol of **2** under the optimized conditions furnished the corresponding product **5a** in 94% yield (2.07 g) (Scheme 1, Figure S1). To illustrate the synthetic utility of the current reaction, we then devoted our efforts to exploring some additional transformations of the vinylogous Henry adduct. As shown in Scheme 1, the dehydration of isoxazole-substituted trifluoromethyl tertiary alcohol **5a** proceeded well with thionyl dichloride and pyridine, affording trifluoromethyl-substituted 3-methyl-4-nitro-5-styrylisoxazole **6** in 90% yield. Using the styrene derivative as a new type of Michael acceptor, the vinylogous 1,6-Michael addition with nitromethane was realized in the presence of DBU. Further studies on asymmetric transformations of **7** are currently under progress in our laboratory.



Scheme 1 Gram-scale synthesis of **5a**



Scheme 2 Transformations of the corresponding Henry product **5a**

In summary, we demonstrated an "on water" direct vinylogous nitroadol (Henry) addition of 3,5-dimethyl-4-nitroisoxazole to aldehydes and trifluoromethyl ketones. The reaction rate was greatly enhanced under "on water" conditions. The process provided a highly efficient and environmentally benign approach for the synthesis of isoxazole-substituted alkanol products. Moreover, the trifluoromethyl tertiary alcohol product could be transformed to the corresponding styrene derivative, which was demonstrated as a new type of Michael acceptor in the vinylogous 1,6-Michael addition with nitromethane.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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