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Synthesis of aza-Henry products and enamines in water by Michael addition of amines or thiols to activated unsaturated compounds

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Abstract

Nitroamines and nitrothiols were synthesized in high yields by the Michael addition of amines and thiols to nitroolefins without using any catalyst. Also, the reaction of amines with dimethylacetylene dicarboxylate (DMAD) in water afforded the corresponding enamines.

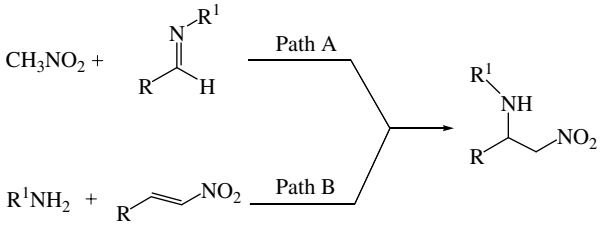
The use of water as a solvent for organic reactions has attracted much attention in synthetic organic chemistry in recent years, not only because water is an environmentally friendly solvent, but also because it exhibits unique reactivity and selectivity, different from those in conventional organic solvents. Thus, the development of novel reactivity and selectivity that cannot be attained in conventional organic solvents is one of the challenging goals of aqueous chemistry.[1]

There are a few reports in the literature on reactions catalyzed by water without using any catalyst, such as the Michael addition of thiols to unsaturated compounds,[2] ring opening of epoxides by amines,[3] the synthesis of dithiocarbamate,[4] and *N*-*tert*-butyloxy-carbonylation of amines.[5] Recently, Ranu and Banerjee investigated the Michael addition of amines to α,β-unsaturated alkenes in water.[6] They showed that the reaction of aliphatic amines with activated unsaturated double bonds was accelerated in water to give high yields of products in short reaction times. They also showed that the reaction of aromatic amines with unsaturated double bonds did not give any product in water.

Herein, we report a direct method for the Michael addition of aromatic amines to nitroolefins in water without using any catalyst. 1,2-Nitroamines are important intermediates for the synthesis of many organic compounds.[7] They can be transformed into 1,2-diamines[8] by reduction,[9] and into α-amino acids by Nef oxidation.[10] 1,2-Nitroamines are typically synthesized by aza-Henry reaction through the addition of nitro compounds to an azomethine function (Scheme 1, path A).

The use of nitroalkenes as Michael acceptors[11] has attracted significant interest in recent years, because of the activating effect of the nitro group, as well as its easy transformation to a number of functional groups. They are also useful starting materials for the synthesis of complex molecules.[12] There are a few reports on the direct addition reaction of amines to nitro-olefins in the literature (Scheme 1, path B).[13,14]

Worrall reported the reaction of aniline with nitroolefins under solvent-free conditions,[15] and showed that



Scheme 1. Methods for the synthesis of aza-Henry products.

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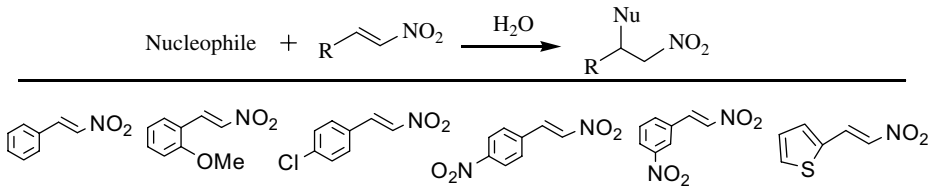
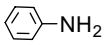
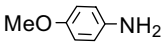
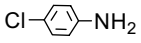
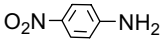
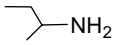
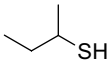
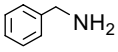
Table 1
Michael addition of amines and thiols with nitroolefins in water without using any catalyst



1 **2** **3** **4** **5** **6**

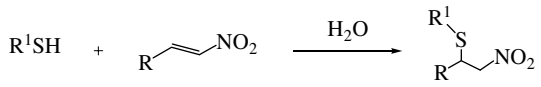
Entry	Nucleophile	Nitroolefin	Yield[a,b] (%)	Entry	Nucleophile	Nitroolefin	Yield[a,b] (%)
1		1	85[15]	21		1	82[13]
2		2	95	22		2	95[13]
3		3	93	23		3	84[13]
4		4	98	24		4	93[13]
5		5	95	25		5	90[13]
6		6	84	26		6	65[13]
7		1	88[15] (H_2O)	27		1	20
8			80 (THF)				
9			74 (CH_2Cl_2)	28		1	98[1]
10			80 (Hexane)	29		2	97[17]
11			90 (Toluene)	30		3	100[17]
12		2	96	31		5	90[1]
13		3	88				
14		4	90	32		1	100
15		5	92	33		2	99
				34		3	74
16		6	70				
				35		5	100
17		1	40[c]				
				36		1	100
18		1	45[c]				
				37		5	92
				38		6	88
19		1	38[15]				
20			23 (CH_2Cl_2)				

[a] Yields based on nitroolefin.
[b] References are given for known compounds.
[c] The yield of imine as reaction product.

p-chloroaniline and *N*-methylaniline do not react with nitrostyrene. This method is not suitable for the preparation of 1,2-nitroamines when the amines and nitroolefins are solids, which is a drawback of this procedure.

As part of our ongoing research devoted to the development of green organic chemistry using water as the reaction medium,[16] we report an efficient, novel, and green procedure for the Michael-type addition of aromatic amines and thiols to activated unsaturated bonds in water without using any catalyst at room temperature in excellent yields.

We initially examined the Michael addition of 4-chloroaniline to nitrostyrene in different solvents. As shown in



Scheme 2. Addition of thiols to nitroolefins in water.

Table 1 (entries 7–11) the yield in water was as high as that in toluene.

We next examined the scope and limitation of this reaction using various aliphatic and aromatic amines with nitroolefins in water. We found that the reaction of aromatic amines with nitroolefins afforded the desired products in excellent yields at room temperature in aqueous medium. Although electron-donating and electron-withdrawing substituents on the phenyl group of nitrostyrene did not have any effect on the yields of the reaction, the Michael reaction of an aniline with a strong electron-withdrawing group, such as nitro, gave a low yield of the adduct (Table 1, entry 27).

When aliphatic amines, such as benzyl amine and *sec*-butyl amine were used as nucleophiles, the imine was the major product (ca. 40%). For secondary aliphatic amines, such as pyrrolidine and piperidine, we did not obtain any of the desired products. It seems that due to the high basicity of the primary and secondary aliphatic amines, decomposition of the nitroolefin to an aldehyde and nitromethane or decomposition of the products occurred. *N*-Methylaniline showed lower reactivity than aniline toward nitroolefins due to steric hindrance, and the yield was 38% in water compared to 23% in CH_2Cl_2.

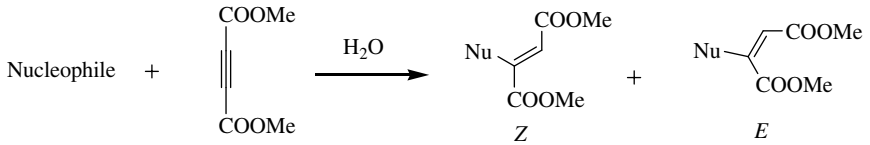
We also attempted the synthesis of an aza-Henry product on large scale (10 g of nitrostyrene and aniline in 100 mL of water). The reaction proceeded well without using any organic solvents for extraction of the product, simply decanting the water gave the crude product in high purity. Further purification by recrystallization from ethanol gave an 86% isolated yield of product.

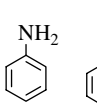
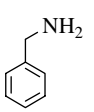
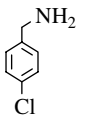
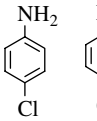
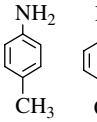
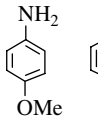
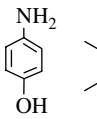
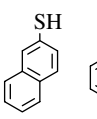
Reactions of thiols with nitroolefins were studied by Cason and coworkers[17] for the preparation of 1,2-nitrothiol compounds using piperidine as a catalyst in organic solvents in yields of about 80%. To the best of our knowledge, there is no report on the synthesis of 1,2-nitrothiols in water. Our study showed that the reaction of thiols with nitroolefins in water gave excellent yields for both aromatic and aliphatic thiols, Scheme 2.

We also investigated the reaction of amines with activated unsaturated bonds in water. Various aliphatic and aromatic amines were reacted with dimethyl acetylenedicarboxylate (DMAD) in water to give the corresponding enamines. The prepared enamines are valuable synthetic intermediates,[18] which are found in a variety of biologically active compounds such as the inhibitor U6751 found in rat liver.[19]

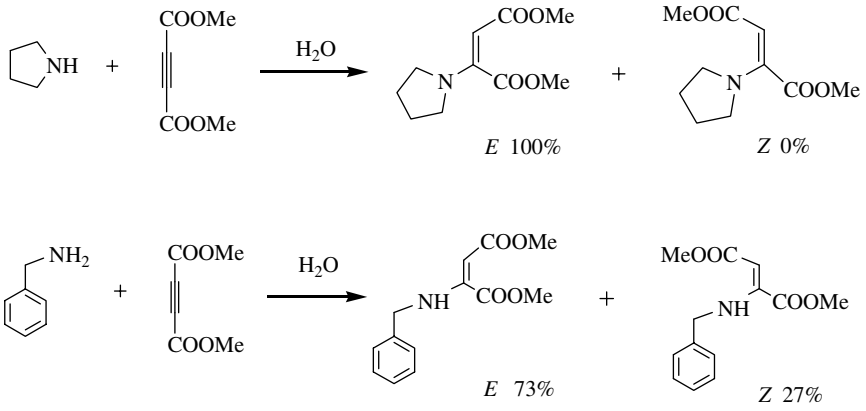
Although there are only a few reports on the addition of amines to DMAD,[18] most used anhydrous methanol, dry ether, or THF as solvent with long reaction times (12–24 h). We found that the reaction of primary and secondary aliphatic and aromatic amines with DMAD was complete in less than 2 h in aqueous medium. The products were stable in aqueous medium. For aromatic amines with different substituents on the phenyl ring, and also *N*-methyaniline, we obtained high yields of products. As shown in Table 2, 2-thionaphthol and 2-butanethiol reacted with DMAD to give products in quantitative yields. In the case of secondary aliphatic amines and aniline derivatives, the ^{1}H NMR spectra showed only one signal for the hydrogen attached to the double bond[18d,e] (4.7 ppm for aliphatic and 5.2 ppm for aniline derivatives in the ^{1}H NMR; 85 ppm for aliphatic amines and 94 ppm for aniline derivatives in ^{13}C NMR). These data indicate that only *E* isomers were formed in these cases which is in complete agreement with the NMR data reported by Dolfini.[20] In the case of primary amines and thiols, ^{1}H NMR spectra showed two singlets at 5.15 and 4.7 ppm for the hydrogen attached to the double bond, which indicated that mixtures of *E* and *Z* isomers were formed (e.g., for benzyl amine the *E*/*Z* ratio was 2.7), Scheme 3. In the case of thiols, the *E* isomer was the major product and the *E*/*Z* ratio for thionaphthol was 0.67 compared to 2-butanethiol with an *E*/*Z* ratio of 0.1.

Table 2
Reaction of aliphatic and aromatic amines and thiols with DMAD in water



Entry	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Nucleophile														
Yield[a,b] (%)	85[18]	100[18]	100[18]	100[18]	100[21]	100[19]	100[19]	99[21]	97[21]	100[21]	84[21]	100[22]	100[22]	100[21]
E/*Z*	*E*	*E*	*E*	*E*	*E*	2.7	1	*E*	*E*	*E*	*E*	0.1	0.67	3.8

[a] Isolated yield.
[b] References are given for known compounds.



Scheme 3. Synthesis of enamines by the addition of amines to DMAD.

In summary, we have developed a highly efficient and environmentally friendly Michael addition reaction of amines and thiols with nitroolefins for the preparation of aza-Henry products and nitrothiol compounds under aqueous conditions. Also, the reaction of amines with DMAD has been investigated in water yielding the corresponding enamines. The metal-free and nonhazardous experimental conditions, room-temperature operation, ease of reaction, short reaction times, and high yields are advantages of this method.

General procedure for the conjugate addition of amines and thiols to nitroolefins and DMAD: In a round bottom flask equipped with a magnetic stirrer, nucleophile (amine or thiol) (6 mmol), nitroolefin or DMAD (5 mmol), and water (20 mL) were charged. Then the reaction mixture was stirred vigorously at room temperature (2 h for DMAD and 4 h for nitroolefins). Extraction of the product with ethyl acetate or CH_2Cl_2 gave the crude product after evaporation. Further purification was achieved by crystallization from ethanol or by column chromatography using ethyl acetate/petroleum ether gradient. It is notable that on large scale no solvent was required for extraction with decanting being sufficient.

Acknowledgment

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