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Aqueous Metal-Free Hydrothiolation of Enamides and Enecarbamates

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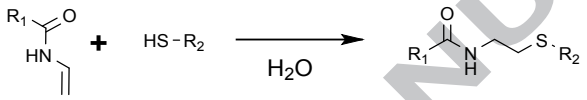
Keywords
Metal-Free
Hydrothiolation
Anti-Markovnikov
Thiol-Ene

Graphical Abstract



Abstract

An efficient and metal-free, anti-Markovnikov selective, hydrothioaltion reaction of enamides and enecarbamates in an aqueous medium is presented. This protocol is operationally simple, mild, and atom-economical. This process provides access to thioethers from available thiols and a variety of enamides and enecarbamates.

Introduction

Hydrothiolation reactions directly couple a thiol and an alkene, two common and abundant building blocks, to form a thioether via a new C−S and C−H bond.[1-3] This strategy toward C−S bond formation is highly valuable because organosulfur compounds are common synthetic intermediates and components of many sulfur-containing natural products.[4-7] Among various hydrothiolation reactions, the thiol–ene reaction, a radical addition of thiols to olefins, is arguably one of the most powerful current methods because of its widespread employment in areas of bioconjugate chemistry, polymer science, and pharmaceutical chemistry.[8,9] Since the first transition metal-catalysed hydrothiolation by Ogawa, organometallic chemists have designed catalytic systems capable of selectively synthesizing C−S bonds from alkynes and allenes.[10-12] On that note, transition metal-catalysed hydrothiolations of alkenes is relatively underdeveloped.[13,14] Ogawa demonstrated the Pd-catalysed hydrothiolation of alkenes bonded directly to heteroatoms, such as vinyl ethers and vinyl lactams.[15] This was followed by the recent

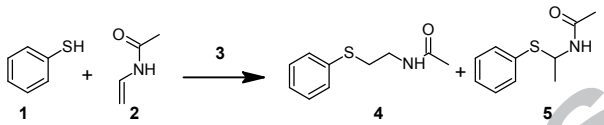
disclosure of the Au-catalysed anti-Markovnikov hydrothiolation of terminal olefins to afford linear C−S bonds.[16] Recently, Hull recently published a rhodium-catalysed regiodivergent hydrothiolation of allyl amines and imines.[17] Yoon has employed photoredox catalysis to achieve the anti- Markovnikov hydrothiolation of alkenes via a thiol−ene reaction.[18] Using this protocol, the hydrothiolation of a variety of styrenes, simple alkenes, and alkynes could be performed.[18,19] Following this methodology, a handful of hydrothiolation reactions or thiol−ene reactions, employing photoredox catalysis have been presented in both functionalization of styrenes or terminal alkenes present in small molecules or polymers.[20-24] In contrast, there have been reports of aqueous anti-Markovnikov addition of thiols to unactivated alkenes [25] We demonstrate here a very simple and green procedure for anti-Markovnikov addition of thiols to enamides and enecarbamates in water without the use of any additives.

Results and Discussion

Our initial interest in hydrothiolation reactions stem from recent advances in the field of photocatalyzed redox intermolecular difunctionalization of alkenes and the different approaches developed.[26] These advances have allowed photoredox catalysis to be considered a suitable process to improve the overall performance of this kind of reaction compared to classic radical initiation conditions.[26] In our preliminary studies, we chose to screen the reaction of thiophenol (**1**) and *N*-vinyl acetamide (**2**) with rhodamine 6G (**3**) as the photoredox catalyst with a variety of organic and aqueous solvents (Table 1, entries 1-10). To our surprise, we could identify and isolate the two regiodivergent hydrothiolation products, **4** and **5** (Table 1). In all the reactions done in aqueous solutions thioether **4**, the expected anti-Markovnikov product, was the only product and was isolated in moderate to good yields. In contrast, when the reaction was done in organic solvents a mixture of thioether **4** and *N*,*S*-acetal **5**, were isolated in low yields. We subsequently decided to explore the reaction conditions associated with the anti-Markovnikov hydrothiolation product. We viewed the potential for a metal free aqueous hydrothiolation reaction as an important and useful methodology for synthetic chemists. In exploring the aqueous hydrothiolation reaction that provided the anti-Markovnikov product **4**, we saw that this reaction was neither visible light nor photoredox catalyst dependent (Table 1, entries 5-10). This data correlates with work done by Ranu, where hydrothiolation reactions were

promoted in water via hydrogen bonding interactions that increase the thiol nucleophilcty.[26] We also observed that the addition of additives like PBS made the reaction worse (Table 1, entry 8). We also found that better yields can be achieved with a slight excess of thiol **1** (Table 1, entry 10). We have determined that we can prepare the anti-Markovnikov hydrothiolation product in water without the use of visible light and a photoredox catalyst.

Table 1. Initial and optimized reaction conditions.



1 2 4 5

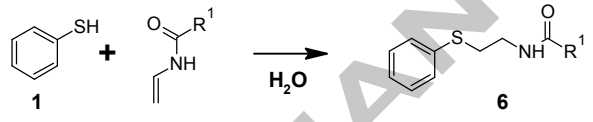
3 = Rhodamine 6G

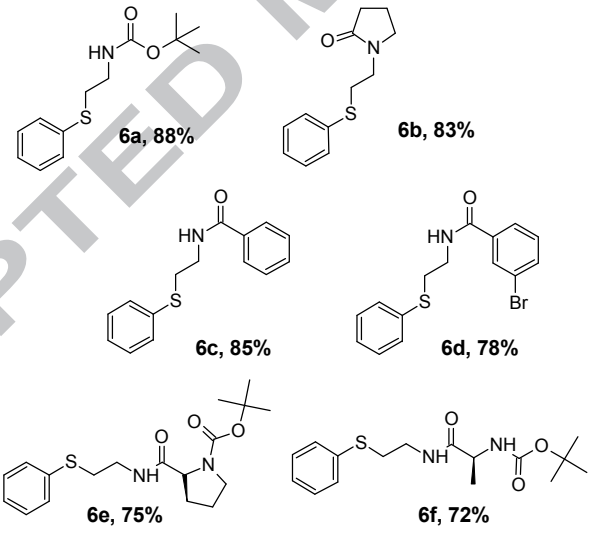
Entry[a]	% Catalyst 3	Blue LED	Solvent	% Yield 4[b]	% Yield 5[b]
1	5%	Yes	ACN	30%	35%
2	5%	Yes	DCM	30%	30%
3	5%	Yes	THF	25%	35%
4	5%	Yes	DMF	22%	25%
5	5%	Yes	10xPBS	50%	0%
6	5%	Yes	H_2O	55%	0%
7	0%	No	ACN	15%	0%
8	0%	No	10xPBS	50%	0%
9	0%	No	H_2O	80%	0%
10[c]	0%	No	H_2O	85%	0%

a. Reactions were run with 1 mmol of **1** and **2** in 0.2 M solvent for 18 hr and monitored by TLC. b. Isolated yields after column chromatography. c. Reaction was run with 1.2 mmol of **1** and 1.0 mmol **2** in 0.2 M H_2O for 18 hr and monitored by TLC.

Next, we proceeded to explore and expand the substrate scope of the currently optimized aqueous anti-Markovnikov hydrothiolation methodology. We discovered in the following experiments that thiophenol (**1**) was a suitable thiol for efficient anti-Markovnikov hydrothiolation to a variety of enamides and enecarbamates in water (Table 2). In all examples, the anti-Markovnikov hydrothiolation products were isolated in moderate to very good yields. This protocol is compatible with the N-Boc-derived enecarbamate (**6a**) and secondary enamide (**6b**)**,** along with primary enamides of varying functionalities from aryl to amino acid derived (**6c-6f**). It should be noted that the reaction is quite compatible with a varying degree of substrates that provide the possibility for further transformations.

Table 2. Results for the hydrothiolation of different enamides and enecarbamates with thiophenol (**1**).

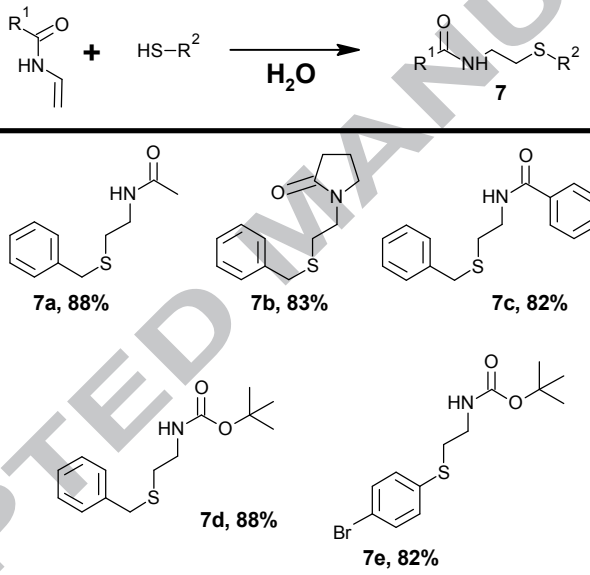




Reactions were run with 1.2 mmol of **1** and 1.0 mmol Enamide or Enecarbamate in 0.2 M H_2O for 18 hr at RT and monitored by TLC. Isolated yields after column chromatography.

Next we turned our attention to explore the reaction substrate scope with respect to variations in the aromatic thiols (Table 3). Benzyl mercaptan was determined to be a suitable thiol for the anti-Markovnikov hydrothiolation reaction with various enamides (**7a**-**7e**). Again these thioether products can be isolated in very good yields. We then explored the use of functionalized aromatic thiols such as bromine (**7f**), with an N-Boc derived enecarbamate. We were pleased to discover that the anti-Markovnikov hydrothiolation products could be isolated in moderate to very good yields (Table 3, **7a-f**). Again, we can demonstrate that this protocol is quite compatible with a varying degree of substrates that provide the possibility for further transformations.

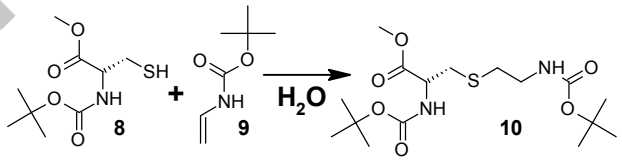
Table 3. Results for the hydrothiolation of different enamides and enecarbamates with varying aromatic thiols.



Reactions were run with 1.2 mmol of Thiol and 1.0 mmol Enamide or Enecarbamate in 0.2 M H_2O for 18 hr at RT and monitored by TLC. Isolated yields after column chromatography.

Although the initial thiols used in the reaction screening process were aromatic. The lab began to investigate the use of alkyl thiols containing various functional groups. Table 4 presents our initial attempts at applying the aqueous anti-Markovnikov hydrothiolaton methodology using N-Boc-Cysteine methyl ester (**8**) and an N-Boc-derived enecarbamate (**9**) (Table 4).Using our previous conditions, initial attempts resulted in poor yields of the desired anti-Markovnikov product **10** (Table 4, entry 1). We decided to explore the effects of extended reaction times and increasing the temperature of the reaction conditions. We found that with an extended reaction time (Table 4, entry 2) there was a slight increase in the isolated yields. However, with gradual increase in the reaction temperature we discovered that moderate to good yields of **10** can be obtained (Table 4, entries 3-5). Notably that at both 57°C (18 hr) and 70°C (2 hr) similar yields of **10** can be isolated depending on the reaction temperature and reaction time chosen. We continued to explore the vinyl amide substrate scope of this hydrothiolation reaction with N-Boc-Cysteine methyl ester (**8**) at 57°C. Table **5** presents the scope of enamide and enecarbamate substrates that were reacted with N-Boc-Cysteine methyl ester (**8**). Again, we found that the anti-Markovnikov hydrothiolation products can be isolated in moderate to good yields from an N-Boc-derived enecarbamate (**10**), a secondary enamide (**11a**)**,** and from primary enamides of varying functionalities from aryl to amino acid derived (**11b-11d**). Unfortunately, when the reaction conditions were applied to reactions using simple alkyl thiols, no desired products were isolated, even with the assistance of elevated temperatures (Table 6, Entries 1-6).

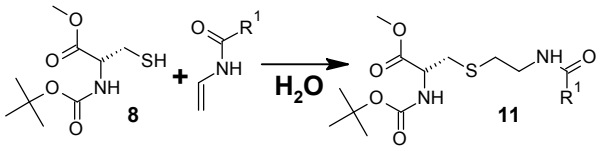
Table 4. Initial and optimized reaction conditions.

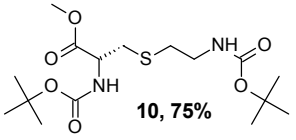


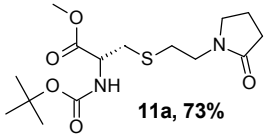
Entry[a]	Time	Temperature	% Yield 4[b]
1	18 hr	RT	10%
2	48hr	RT	35%
3	18 hr	37°C	65%
4	18 hr	57°C	75%
5	2 hr	75°C	75%

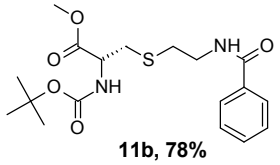
a. Reactions were run with 1.2 mmol of **8** and 1.0 mmol of **9** in 0.2 M H_2O and monitored by TLC. b. Isolated yields after column chromatography.

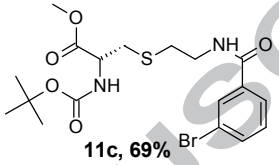
Table 5. Results for the hydrothiolation of varying enamides and enecarbamates with N-Boc-Cysteine methyl ester (**8**).

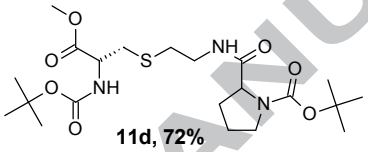






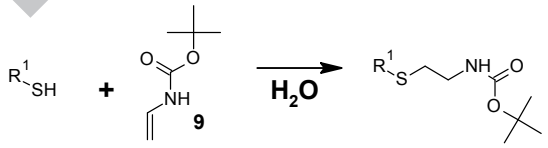






Reactions were run with 1.2 mmol of **8** and 1.0 mmol Enamide or Enecarbamate in 0.2 M H_2O for 18 hr at 57 °C and monitored by TLC. Isolated yields after column chromatography.

Table 6. Reactions with alkyl thiols.

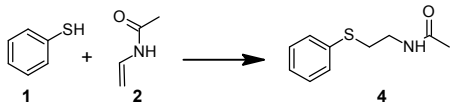


Entry[a]	R^1	Temperature	% Yield 4
1	Ethyl	RT	NR
2	Isopropyl	RT	NR
3	Octyl	RT	NR
4	Ethyl	75°C	NR
5	Isopropyl	75°C	NR
6	Octyl	75°C	NR

a. Reactions were run with 1.2 mmol of **8** and 1.0 mmol of **9** in 0.2 M H_2O and monitored by TLC.

On the basis of the above results and related literature, we believe that water has a specific role in this reaction (Scheme 1).[18,19,25] In our initial reactions we found that the anti-Markovnikov hydrothiolation product (**4**) for the reaction of thiophenol (**1**) to N-vinyl acetamide (**2**) in acetonitrile was isolated in 15% yield after 18 hours (Table 1, entry 7). In contrast, when the reaction is run in water for 18 hours the anti-Markovnikov hydrothiolation product (**4**) is isolated in 80% yield (Table 1, entry 9). In order to explore the mechansim in more depth a series of reactions were done. Initial reactions were set up to explore the possibility of a radical based mechansim (Table 7, Entries 1 and 2). Under standard AIBN condition the anti-Markovnikov hydrothiolation product (**4**) was isolated at 45% yield. When the control experiment without AIBN was done only 12% of **4** was isolated. Reactions run in other organic solvents without radical initators and light were explored. Hydrothiolation product **4** was isolated in poor to moderate yield in these entries (Table 7, Entries 3-7) likely by a standard alkene addition mechanism. None of these entries (Table 7, Entries 3-7) performed as well as when water was the solvent (Table 7, Entries 10). It was also determined that acidic and basic aqueous conditions resulted in no reation (Table 7, Entries 8 and 9). A competition experiment was also done between a 1:1 mixture thiophenol and 4-bromo-thiophenol (Table 8). We found that both anti-Markovnikov hydrothiolation product **4** and **7e** can be isolated in a 4:1 ratio. From these results we believe that water has a specific and important role in improving this reaction. We also looked at other possible nucleophiles with similar pKa profiles to thiophenol (**1**). Unfortunately, when the reaction conditions were applied to these potential nucleophiles, no desired products were isolated (Table 9, Entries 1-3). A plausible mechanism involves water promoting the reaction through hydrogen bond formation with the hydrogen of the thiol, thus increases the nucleophilicity of the thiolate ion. It may be further speculated that addition of the thiolate anion to the enamide takes place in a concerted manner with steric factors controlling the regioselectivity leading to the anti-Markovnikov product (Scheme 1).[25]

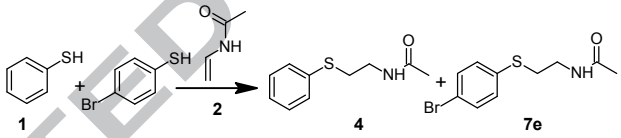
Table 7. Reactions to explore the hydrothiolation mechansim.



Entry[a]	Additives	Solvent	% Yield 4[b]
1	AIBN	Toluene	40%
2	None	Toluene	15%
3	None	THF	25%
4	None	DMF	15%
5	None	MeOH	35%
6	None	ACN	55%
7	None	DCM	45%
8	None	2M NaOH	NR
9	None	3M HCl	NR
10	None	H_2O	85%

a. Reaction was run with 1.2 mmol of **1** and 1.0 mmol **2** in 0.2 M H_2O for 18 hr and monitored by TLC. b. Isolated yields after column chromatography.

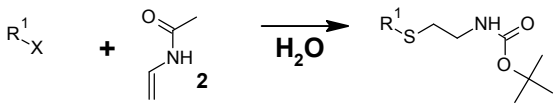
Table 8 . Competition reaction.



Entry[a]	Solvent	% Yield 4	% Yield 7e
1	H_2O	64%	16%

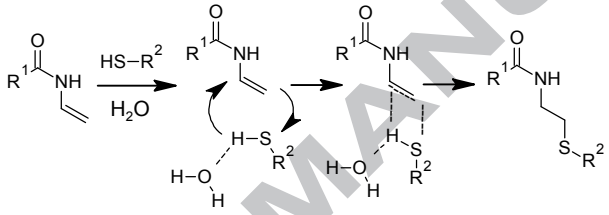
a. Reaction was run with 1.2 mmol of **1** and 1.0 mmol **2** in 0.2 M H_2O for 18 hr and monitored by TLC. b. Isolated yields after column chromatography.

Table 9 . Hydrothiolation reaction with other nucleophiles.



Entry[a]	X	Temperature	% Yield 4
1	Phenol	RT	NR
2	Aniline	RT	NR
3	MeO-Ala-NH_2 HCl	RT	NR

a. Reactions were run with 1.2 mmol of **8** and 1.0 mmol of **9** in 0.2 M H_2O and monitored by TLC.



Scheme 1. Proposed mechanism for the aqueous hydrothiolation reaction.

Conclusion

In conclusion, we have developed a very simple and efficient metal-free methodology for the addition of thiols to enamides and enecarbamates in water without any additives producing the anti-Markovnikov thioether products. The significant advantages offered by this method are simple operation, mild and environmentally friendly experimental conditions that are compatible with various functionalities, anti-Markovnikov regioselectivity, and moderate to very good yields of isolated thioether products. This methodology thus provides a very convenient and synthetically useful approach to preparing chemically useful thioethers. Further studies on the application of this methodology to the thiol selective conjugation of enamides and enecarbamates to Cysteine containing peptides and proteins are currently in progress.

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

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Highlights

- An efficient and metal-free thiol-ene reaction.
- Anti-Markovnikov selective thiole-ene reaction.
- Hydrothioaltion reaction of enamides and enecarbamates in an aqueous medium is presented.
- This protocol is operationally simple, mild, and atom-economical.
- This process provides access to thioethers from available thiols and a variety of enamides and enecarbamates.