Click Chemistry

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Organocatalytic, Regioselective Nucleophilic "Click" Addition of Thiols to Propiolic Acid Esters for Polymer–Polymer Coupling**

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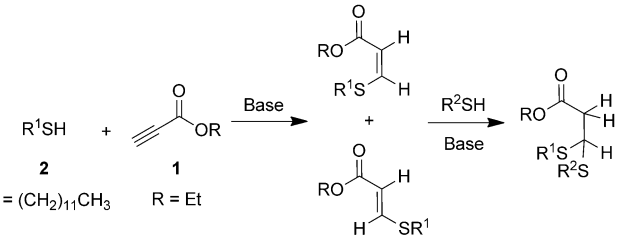
The hydrothiolation of a C=C bond, commonly referred to as a thiol-ene addition reaction, has been investigated extensively for use in many areas of organic synthesis and materials chemistry because of its "click" characteristics, which include a rapid, quantitative, and selective reaction with a minimum number of side reactions.[1] The thiol-ene reaction proceeds by radical or nucleophile-catalyzed addition. The former route follows an anti-Markonikov rule and is initiated by thermal[2] or UV irradiation,[3] while the latter route requires an electron-deficient alkene,[2,4] that is, a C=C bond with an adjacent electron-withdrawing group, such as ester, amide, or cyanide. Although the nucleophilic thiol-ene addition is restricted by the availability of the activated alkenes, it has the benefits of mild reaction conditions, no detectable by-products, and high conversion under optimized conditions.[4a] In addition, this reaction can be readily catalyzed by a range of nucleophilic catalysts, such as primary/secondary amines[4a,5] and several phosphines.[6] The nucleophilic thiol addition has therefore been utilized in polymer chemistry for the functionalization of end groups or side chains,[2,4b,c,7] polymer–polymer coupling,[8] polymer–protein bioconjugation,[9] and the preparation of hydrogels.[10]

The thiol-yne addition is very similar to the radical thiol-ene reaction in terms of reaction conditions and mechanism. The addition of a thiol to an alkyne can be initiated by radicals, and gives a mixture of *E*/*Z* alkenes when one equivalent of thiol is used, or a bisthioether when two equivalents of thiol(s) are used.[11] In recent years, this reaction has been used in the preparation of highly functionalized linear polymers[12] and highly branched polymer structures, such as multifunctional brush polymers,[13] dendrimers,[14] glycosylated poly(phoshazine)s,[15] and highly cross-linked polymer networks.[16] Similar to the radical thiol-ene addition, the radical thiol-yne addition also has the disadvantage of forming reactive intermediates during the radical process, resulting in unavoidable side reactions.[17] On the other hand, while the thiol-yne radical addition has been broadly investigated, the nucleophilic addition of thiols across triple bonds has received significantly less attention.[18] In previous studies, the addition of thiolates to activated alkynes, including propiloic acid esters[18a–e] and strained cyclo-octynes,[18f] has been investigated. In the former case, some selectivity has been achieved using aryl thiolates and alkyne esters with specific directing groups,[18e] however, regioselectivity with alkyl thiols, which form thioacrylate units that may be useful intermediates in fused β-lactam antibiotics, has been shown to be pH-dependent in aqueous conditions.[18c,e] Herein, we report the base-catalyzed addition of alkyl thiols to electron-deficient alkynes with high levels of regioselectivity that can be directed based on the choice of catalyst and solvent. Furthermore, we report both the selective single and double addition of thiols and demonstrate the utility of this reaction in end-group modification and coupling of polymers.

Our initial investigation focused on the equimolar reaction of the small-molecule models ethyl propiolate (**1**) and dodecane-1-thiol (**2**; Scheme 1). A range of catalysts were tested for the hydrothiolation of **1** with **2** in chloroform



Scheme 1. Base-catalyzed addition of dodecane-1-thiol (**2**) to ethyl propiolate (**1**).

(Table 1). Triethylamine was shown to be a highly efficient catalyst for the addition at a concentration of 10 mol% (entry 5). ^{1}H NMR spectroscopic analysis showed the complete disappearance of the alkyne proton signal and the appearance of alkene proton signals within 2 h (Figure S1 in the Supporting Information). Interestingly, the bisthioether product was not obtained, even when an excess amount of thiol was used. Remarkably, the reaction was highly regioselective; in the ^{1}H NMR spectrum, the alkenyl protons of the major product (97% yield) featured a vicinal coupling constant ($^3J_{HH}$) of 15 Hz, which is typical for *trans* isomers.[19]

A change of the catalyst concentration significantly influenced the reaction time (Figure S2 in the Supporting Information), but did not affect the regioselectivity of the reaction or lead to any side products. Surprisingly, secondary

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Table 1: Effect of catalyst on thiol-yne addition.[a]

Entry	Catalyst	*t* [min]	Conv.[b] [%]	*cis* [%]	*trans* [%]
1	n-hexylamine	60	0	0	0
2	isopropylamine		0	0	0
3	diisopropylamine	60	<1	50	50
4	dicyclohexylamine	60	<1	50	50
5	NEt_3	60	85	3	97
6	DIPEA	60	<1	50	50
7[c]	DBU	10	100	80	20
8[d]	TBD	10	100	90	10
9[c]	$PPhMe_2$	10	100	50	50
10[c]	PPh_3	60	20	70	30

[a] Reaction conditions: [alkyne]:[thiol]:[cat.] = 1:1.2:0.1, [alkyne] = 0.1 M in $CDCl_3$. [b] Calculated based on integration in the ^{1}H NMR spectrum. [c] [alkyne]:[thiol]:[cat.] = 1:1.2:0.01. [d] [alkyne]:[thiol]:[cat.] = 1:1.2:0.001. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA = diisopropylethylamine; TBD = 1,5,7-triazabicyclo[4,4,0]dec-5-ene.

amines only poorly catalyzed the reaction compared with NEt_3, and primary amines did not show any catalytic activity (Figure S3 in the Supporting Information). This observation is in contrast to the nucleophilic addition of thiols to activated alkenes, in which primary amines are much more efficient catalysts than tertiary amines, such as NEt_3.[1b] It is noteworthy that most of the chosen amine catalysts have very similar pK_a values, and it is thus likely that the basicity of the catalyst is not the main cause of its reactivity in these reactions. The bulkier tertiary amine diisopropylethylamine (DIPEA; Table 1, entry 6) also did not show any catalytic effect, despite its increased basicity compared to NEt_3 (pK_a(DIPEA) = 11.4 versus pK_a(NEt_3) = 10.7), thus suggesting that steric hindrance is a major factor for the reactivity of the catalysts.

Several bases, including 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; entry 7) and 1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD; entry 8), which are an amidine and a guanidine derivative, respectively, and phosphines (entries 9 and 10) were also investigated as catalysts for this reaction. The catalytic activity of DBU was an order of magnitude higher than that of NEt_3. The conversion of **1** was complete in less than 10 min with 1 mol% of DBU and a 1:1 molar ratio of thiol to alkyne (Figure S4 in Supporting Information). TBD showed even greater catalytic activity than DBU, with complete conversion of the alkyne starting material to the alkene product in less than 10 min with only 0.1 mol% of the catalyst. In the presence of excess thiol, formation of bisthioether was also observed with 1 mol% TBD (Figure S6 in the Supporting Information). Interestingly, both the DBU- and TBD-catalyzed addition of thiol **2** to alkyne **1** resulted in the *cis* isomer as the major thioalkene adduct, as indicated by the alkenyl proton signals in the ^{1}H NMR spectra of the products displaying a $^3J_{HH}$ of 10 Hz.[19] Reactions with non-nitrogen-containing catalysts were also investigated. $PPhMe_2$, which is a very effective catalyst for nucleophilic thiol-ene addition,[4a,6a] was also very effective for the thiol-yne addition with complete conversion of the starting materials in less than 10 min (entry 9). Notably however, in this case, a *cis*:*trans* product ratio of 1:1 was observed (Figure S6 in Supporting Information). Finally, PPh_3 proved to be a less effective catalyst compared with $PPhMe_2$ (entry 10), as may be expected on both basicity and steric grounds. After 60 min, a conversion of only 20% and a *cis*:*trans* ratio of 7:3 was obtained.

Further studies focused on the investigation of the influence of solvent polarity on the regioselectivity of the system (Table 2). A transition of the *cis*:*trans* ratio was observed as the polarity of the solvent increased (Figure S8 in Supporting Information). In nonpolar solvents, such as benzene and chloroform, the dominant product was the *trans* isomer (*trans*:*cis* = 98:2 in benzene, entry 1), while in highly polar solvents, such as acetonitrile and DMSO, the major product was the *cis* isomer (*trans*:*cis* = 22:78 in DMSO, entry 8). Furthermore, the polarity of the thiol substrate also affected the regioselectivity of the reaction; the use of 1-mercaptoethanol in place of **2** led to an increased formation of the *cis* isomer, thus indicating that the polarity of the overall solution is critical to the regioselectivity of the reaction. Notably, the reaction also proceeded under solvent-free conditions with the reagents in a molar ratio of 1:1 and NEt_3 as catalyst. Evaporation of NEt_3 in vacuo from this mixture led to the product quantitatively with a *trans*:*cis* ratio of 37:63. Performing the reaction in more polar solvents, such as methanol (Figure S9 in the Supporting Information) and water, was also highly efficient (Table 2, entry 9–11), a result that is consistent with previous reports.[18c]

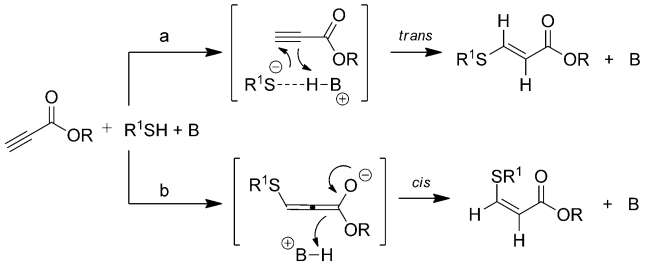
Table 2: Effect of solvent on thiol-yne addition.[a]

Entry	Solvent	Thiol	Conv.[b] [%]	*cis* [%]	*trans* [%]
1	C_6H_6	1-DT	50	2	98
2	$CHCl_3$	1-DT	96	3	97
3	$CHCl_3$	2-ME	100	21	79
4	$(CH_3)_2O$	1-DT	100	48	52
5	CH_3CN	1-DT	100	66	34
6	CH_3CN	2-ME	100	98	2
7	CH_3CN	1-DT	3	65	35
8	DMSO	1-DT	100	78	22
9[c,d]	MeOH	2-ME	100	53	47
10[c,d]	H_2O	2-ME	100	67	33
11[c,d]	H_2O[e]	2-ME	100	94	6

[a] Reaction conditions: [alkyne]:[thiol]:[TEA] = 1:1.2:0.25 [alkyne] = 0.1 M, reaction time = 10 min. [b] Determined by ^{1}H NMR spectroscopy after quenching the reaction mixture with *p*-TsOH. [c] No catalyst was used. [d] Poly(ethylene glycol) bispropiolate was used as the alkyne compound. [e] Phosphate-buffered saline (pH 7.8) was used. DMSO = dimethyl sulfoxide; 1-DT = dodecane-1-thiol; 2-ME = 2-mercaptoethanol.

To demonstrate the possibility to change the regioselectivity of this reaction, the NEt_3- and DBU-catalyzed reactions of **1** with **2** in a molar ratio of 1:1 in chloroform and acetonitrile, respectively, were compared. The very high selectivity of the reactions enabled the purification of the products by a simple acid wash (to remove catalyst) and solvent evaporation to give the *trans* and *cis* thiol-yne addition products in 96% (with NEt_3 in chloroform) and 91% (with

DBU in acetonitrile) yield of isolated product, respectively. We postulate that the origin of this regioselectivity is the ion pairing of the protonated base and thiolate anion in solution. As such, in apolar solutions with weaker bases, the thiol and catalyst behave as a hydrogen-bonded pair so that attack and protonation take place from the same side (Scheme 2a) to produce the *trans* isomer, whereas in more polar solvents and with stronger bases, isolated thiolate anions obey the anti-addition rule to produce the *cis* isomer (Scheme 2b).[18e]



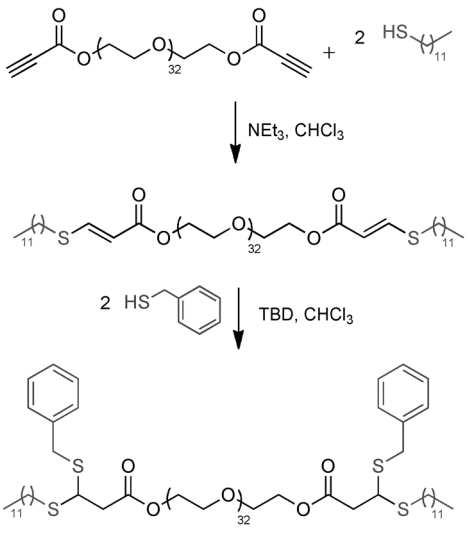
Scheme 2. Proposed mechanism for regioselective base-catalyzed thiol-yne addition. a) Apolar solvent and/or weak base; b) polar solvent and/or strong base.

It has been previously reported that β-sulfido-α,β-unsaturated carbonyl compounds (vinyl sulfide carbonyl (VSC) compounds) can undergo reversible and fast thiol exchange in the presence of a second thiol and NEt_3 as catalyst.[20] We therefore carried out a series of experiments to examine the possibility of thiol exchange in the VSC product from the thiol-yne addition. Reaction of **1** with two molar equivalents of **2** in $CDCl_3$ with either NEt_3 or DBU as catalyst led to only the formation of the single-addition product. Surprisingly, no bisthioether product, which would result from the double addition of thiol across the triple bond, was observed even after heating the above mixture at 60 °C for 24 h or subjecting it to UV irradiation for over 3 h. Furthermore, no *cis*/*trans* isomerization was observed in this reaction mixture, which indicated that the VSC products obtained are stable in the presence of catalyst and excess thiol. In a further experiment with TBD as the catalyst, benzylmercaptan was added to the VSC single-addition product from the reaction of **1** and **2** to produce the hetero-bisthioether product (Scheme 1). HPLC and TLC analysis (Figures S11 and S12 in the Supporting Information) of the obtained product showed only a single fraction that was observed at a different retention time to either homo-bisthioether addition product, which indicates that thiol exchange does not occur in the presence of TBD. These results clearly demonstrate the 'click' characteristics of the present method, including single-reaction trajectory and formation of a stable product.[21]

Taking advantage of the robust and efficient nature of the thiol-yne addition, we attempted to apply this reaction to the end-group modification of macromolecules, namely poly(ethylene glyol)s, PEGs. Firstly, PEG_{32}-bispropiolate was synthesized by the simple Fischer esterification of bishydroxy-terminated PEG with propiolic acid. The polymer product was then end-functionalized with several commercially available thiol compounds using either NEt_3 (10 mol%) or DBU (1 mol%) as the catalyst. The ratio of [alkyne]:[thiol] was kept at 1:1.02 to take account of the difficulty in accurately assessing the end-group concentration in the polymeric alkynes. *Cis*:*trans* product ratios were consistent with those observed for the reactions of the small alkyne and thiol molecules (Figures S13–S16 in the Supporting Information), and size-exclusion chromatography (SEC) traces of the polymers showed a distinct shift to lower retention times, thus indicating that a reaction had indeed occurred at the chain ends (Figure S14 in the Supporting Information).

To extend the applicability and demonstrate a broader substrate scope of this type of 'click' chemistry in the end-group modification of polymers, we also synthesized PEG_{32}-bispropiolamide and functionalized it with thiol compounds under similar conditions as applied to the reaction of PEG_{32}-bispropiolate with thiols. The rate of the thiol addition to the propiolamide with of NEt_3 (0.1 equiv) in $CDCl_3$ was significantly smaller than the rate of thiol addition to the propiolate, with only around 20% conversion of the propiolamide end group after 10 h. End-group modification of PEG_{32}-bispropiolamide with a thiol compound using DBU (0.05 equiv) as catalyst remained fast and efficient with complete conversion observed in 10 min, as indicated by ^1H NMR spectroscopy and SEC (Figures S18 and S19 in the Supporting Information). The regioselectivity of the thiol addition to the propiolamide was found to be similar to that of the thiol addition to the propiolate with NEt_3 and DBU as catalysts. Furthermore, complete dithiol addition to the propiolamide to form the dithiane product was also observed when TBD (0.05 equiv with regard to the propylamide group) was used as the catalyst.

The enhanced reactivity of TBD in the catalysis of the second thiol-ene addition was also utilized to orthogonally functionalize alkyne bonds with different thiols (Scheme 3). To this end, following the NEt_3-catalyzed addition of dodecane-1-thiol (**2**) to the PEG_{32}-bispropiolate, benzylmercaptan (2 equiv with regard to the alkene) and TBD (1 mol%) were added to the reaction mixture. Complete conversion of the end group of the polymer after 10 min was indicated by the



Scheme 3. Sequential addition of thiols to PEG-bispropiolate.

disappearance of the alkene proton signals in the ^{1}H NMR spectrum, and the complete shift of the SEC traces to lower retention times (Figures S15 and S20 in the Supporting Information).

To further demonstrate the utility of this approach in polymer chemistry, a PEG_{12}-monothiol was coupled to the PEG_{32}-bispropiolate with alkyne:thiol in a stoichiometric ratio, 10 mol % of NEt_3, and a polymer concentration of 0.1 M in $CDCl_3$. Analysis by both ^{1}H NMR spectroscopy, which showed the complete conversion of the alkyne in less than 10 min, and SEC, which did not show a trace of the starting material, indicated an extremely fast and efficient polymer–polymer coupling (Figure 1, and Figure S21 in the Supporting Information). Extension to the coupling of a PEG_{125}-mono-

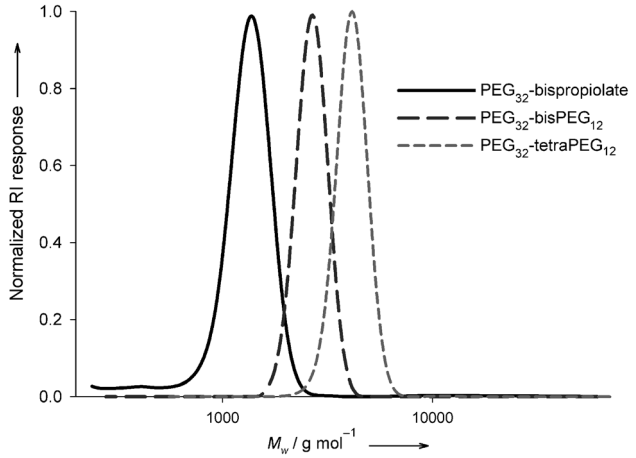


Figure 1. SEC traces of the $PEG_{1.5k}$-bispropiolate and the polymer products.

thiol with a higher molar mass, to the PEG_{32}-bispropiolate to form PEG_{32}-bisPEG_{125} was also demonstrated to be fast and efficient as determined by ^{1}H NMR spectroscopy and SEC (Figure S22). The second functionalization of the PEG_{12}-bisPEG_{32} polymer was also undertaken using TBD as catalyst to form an H-shaped polymer by the addition of another PEG-monothiol to the formed alkene (Figure S23 in the Supporting Information) and also for the addition of thioglycerol (Figure S24 in the Supporting Information), which resulted in a PEG with hydroxy groups at specific, defined points along the polymer chain. These results clearly demonstrate the potential of the base-catalyzed thiol-yne nucleophilic addition reaction in polymer–polymer coupling and the preparation of polymers with specific architecture and functional groups.

In conclusion, we have demonstrated that the regioselective addition of alkyl thiols to an electron-deficient alkyne can be carried out in organic and aqueous media with the regioselectivity controlled by selecting a suitable catalyst/solvent system. Furthermore, the ability to readily transform end groups of polymers and selectively perform the second addition of thiols enables the synthesis of complex macromolecules with this methodology. Further investigations to understand the mechanism of the addition and the origin of regioselectivity as well as to further demonstrate the utility of this reaction in polymer and materials chemistry are currently under way.

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