Salt-Free CatAnionic Vesicular Nanoreactor from Dithiocarbamate: Michael Addition of Nitroolefins in Aqueous Vesicle System

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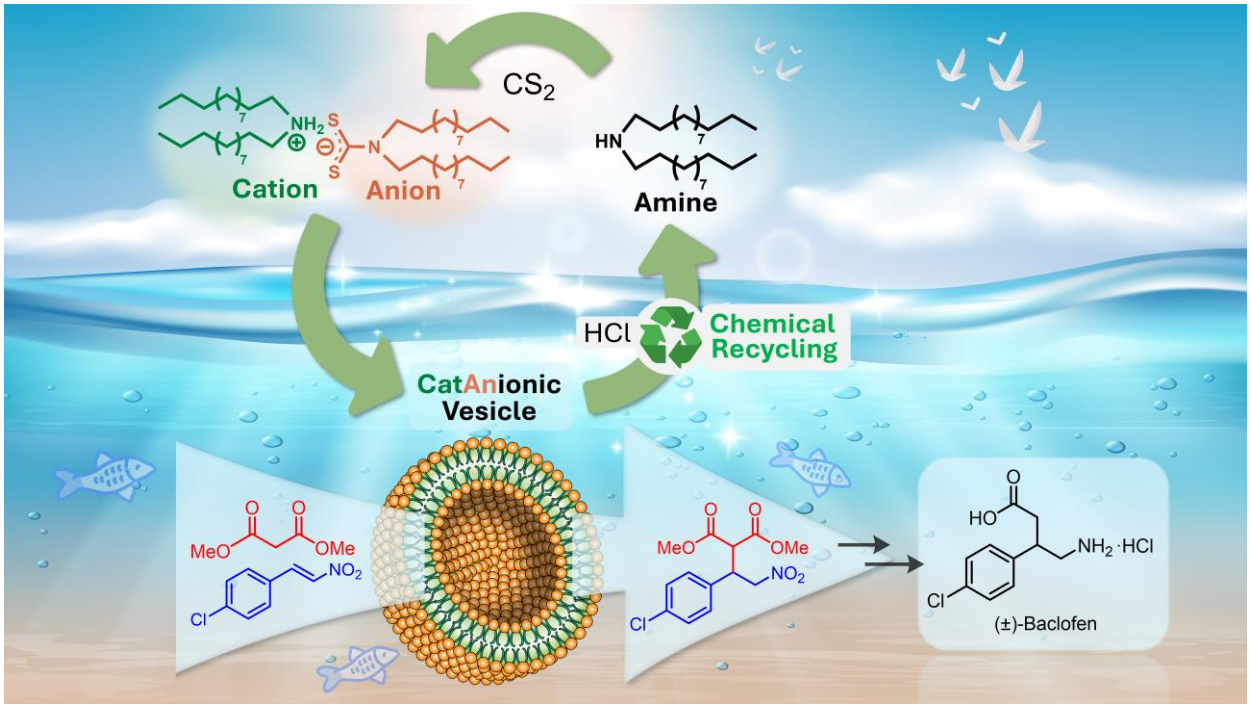
Graphical Abstract



Abstract

The salt-free CatAnionic vesicle was previously generated by mixing cationic and anionic amphiphiles, and removing the salt that occurred as a side product from the mixture. In this study, we report a new strategy to produce the salt-free CatAnionic vesicle of *N*,*N*-dialkylamonium *N*,*N* dialkyldithiocarbamate (AmDTC) through a one-step condensation between secondary amine and carbon disulfide. Both dialkylammonium cationic and dithiocarbamate anionic amphiphiles were generated concurrently during the condensation. The AmDTC was dispersed in water, resulting in the spontaneous formation of salt-free CatAnionic vesicles. Among several AmDTCs, the *N*,*N*-didodecylamonium *N*,*N*-didodecyldithiocarbamate (**AmDTC-$C_{12}C_{12}$**) showed high stability and was applied as a vesicular nanoreactor for the Michael addition in water. Michael addition in an aqueous system between nitroolefins and 1,3-dicarbonyl compounds afforded the desired twenty-three Michael adducts, with yields ranging from 65% to 92%. It is hypothesized that the **AmDTC-$C_{12}C_{12}$** serves as a vesicular nanoreactor and plays a role in catalysis at the dithiocarbamate functional group. Preparative-scale and one-pot Michael addition by *in situ* generation of **AmDTC-$C_{12}C_{12}$** vesicle afforded the Michael adducts also in good yields. The **AmDTC-$C_{12}C_{12}$** vesicular nanoreactor was applied for the synthesis of (±)-baclofen with 54% yields over three steps. The reusability of the **AmDTC-$C_{12}C_{12}$** was demonstrated and allowed the reuse of the CatAnionic vesicle up to seven cycles. Finally, chemical recycling was demonstrated by converting **AmDTC-$C_{12}C_{12}$** to *N*,*N*-didodecylammonium chloride by simple acidification.

Introduction

Self-assembly is a natural process that takes place at many scales. It refers to the spontaneous organizing of constituents into structures or patterns without the need for human involvement. The interest in self-assembly stems from its capacity to generate order from a state of disorder. Self-assembly plays an essential role in biological systems and is being applied to applications in the fields of chemistry, nanotechnology, and robotics.[1] Chemical conversions in nature occur in confined environments, leading to significant improvement in conversion efficiency. This coupling of chemicals in nature is observed across a range of sizes, from nanometer-sized enzymes to micrometer-sized cells. This has inspired synthetic chemists to create similar confined reaction environments to mimic these processes.[2] Traditionally, synthetic approaches involved the complex multistep synthesis of low molecular weight catalysts, which could impose restrictions on scalability. Alternatively, a different approach involves the self-assembly of small molecular components constitute into structures like micelles and vesicles. These self-assemblies provide controlled environments for chemical reactions, influencing reaction pathways and product yields. Therefore, the utilization of synthetic vesicles and micelles as nanoreactors for chemical synthesis, which replicate nature's efficiency, is greatly desirable.[3-5]

In general, systems that generate vesicles can be classified into three main types according to their chemical composition. First, vesicles produced from synthetic or natural phospholipids (liposomes), which consist of double-chained hydrocarbon and zwitterionic ions of phosphodiester linkage. These are widely studied and used in various applications due to their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic substances.[6] Second, vesicles generated from double-chained cationic or double-chained anionic amphiphiles. The double-chained cationic amphiphiles are commonly in a class of quaternary ammonium salts. Among these salts, didodecyldimethylammonium bromide (DDAB) is the most studied.[7] For the double-chained anionic amphiphile, the frequently used amphiphile is sodium bis(2-ethylhexyl)sulfosuccinate (AOT).[8] Third, cationic and anionic (CatAnionic) vesicles are formed in aqueous mixtures of oppositely charged single-chained amphiphiles.[9] The strong electrostatic interaction of the ionic bond between the single-chained cationic and single-chained anionic amphiphiles could be viewed as a pseudo-covalent bond, and this system is identified as pseudodouble-chained amphiphiles. The balance of charges between the CatAnionic amphiphiles results in a cylinder-like shape, and they do not pack into globular micelles like their parent single-chained amphiphiles. Instead, they spontaneously rearrange themselves into a stable bilayer of vesicles through self-assembly.[10]

The formation of CatAnionic vesicles is thermodynamically stable and spontaneous, requiring no external force, in contrast to others, such as phospholipid vesicles.[11] However, when the ratio between the cationic and anionic amphiphile in the mixture is precisely one-to-one (with an equal amount of both amphiphiles), it is common to observe the formation of precipitates.[12, 13] The precipitation of amphiphiles occurs due to the formation of side product-salt, which is generated by the (small) counterions inherent in both amphiphiles. The presence of a side product-salt increases the ionic strength and reduces the electrostatic repulsion between vesicles, leading to the aggregation of the CatAnionic vesicles.[14] In order to reduce the precipitation, salt-free CatAnionic vesicles (also known as 'true' CatAnionic vesicles or ion-pair amphiphiles) are produced by removing or purifying the side product-salt from the mixture using extraction or dialysis.[15] As a result, the salt-free CatAnionic system observed low conductivity and ionic strength. The electrostatic repulsion between CatAnionic vesicles is restored, thus increasing the stability of the system. Due to this factor, the salt-free CatAnionic systems can be prepared at higher concentrations, without precipitates, at the stoichiometric ratio compared to the CatAnionic systems that contain salt.[16]

In classical organic synthesis, organic solvents play a significant role in dissolving the reactants and promoting chemical reactions. Petroleum-based organic solvents are regarded as indispensable mediums for organic synthesis. Nevertheless, the utilization of organic solvents presents certain limitations, such as hazardous impacts on humans and the environment and the high cost of proper disposal.[17, 18] The utilization of water as a reaction medium has emerged as an alternative since it benefits from environmental friendliness, safety, and low cost.[19] Water possesses many unique physical and chemical properties, such as high heat capacity, large dielectric constant, extensive hydrogen bonding, and a wide liquid temperature range.[19, 20] Despite these potential advantages, water is not commonly used as the sole solvent in organic

synthesis. This is primarily because most organic compounds do not dissolve well in water, and solubility is considered essential for reactivity.[20]

Amphiphilic molecules undergo spontaneous self-assembly in aqueous environments, forming micelles and vesicles. These structures have diverse applications in drug delivery[21] (encapsulating drugs for targeted release) and detergency[22, 23] (solubilizing dirt particles). However, the utility of amphiphiles extends beyond mere encapsulation. Within the realm of modern organic synthesis, they can function as nanoreactors.[24] This approach offers an efficient strategy for conducting organic syntheses in an aqueous medium. Single-chain amphiphiles, typically micelles, offer simplicity in their structures and can encapsulate hydrophobic molecules within their core.[25] These micellar systems have found application in a diverse range of reactions, as depicted in **Figure 1a**. For instance, our previous work achieved ozonolysis in water using Coolade as a low-foaming nonionic micellar system, allowing ozonolysis to perform in an aqueous medium.[26] Hoven's group employed micellar nanoreactors derived from nonionic polymeric amphiphiles to enable thia-Michael addition in water.[27] Various research groups have explored the combination of catalysts and micelles. Cationic amphiphiles, in conjunction with catalysts, facilitated asymmetric transfer hydrogenation (ATH)[28] and Morita-Baylis-Hillman reaction (MBH)[29] in water. Lipshutz's group showcased metal-catalyzed cross-coupling reactions in water, accelerated by a micellar system of nonionic amphiphiles (TPGS-750-M) [30] Additionally, rhodium-catalyzed hydrogenation was performed within the micellar system of both nonionic and anionic amphiphiles.[31] Furthermore, the decorations of catalytic sites on amphiphiles were shown to generate micelles that functioned as catalysts. For instance, Hayashi's group reported a proline-amphiphile incorporating a proline unit and long alkyl chain to facilitate the cross-aldol reaction.[32] Here, the proline moiety acts as the catalyst, while the long alkyl chain promotes micellar formation. Next, Cheng's group carried out the Michael addition using a surfactant-type asymmetric organocatalyst (STAO).[33] The headgroup of the STAO serves as the catalyst, while the amphiphilic moiety enhances the reaction time and yields.

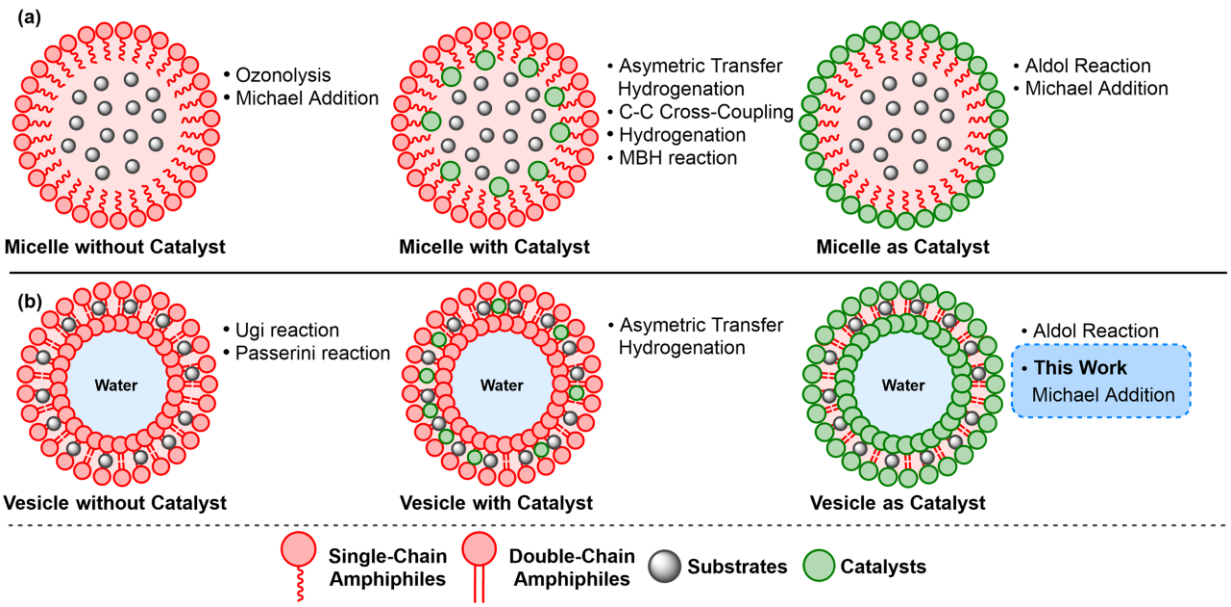
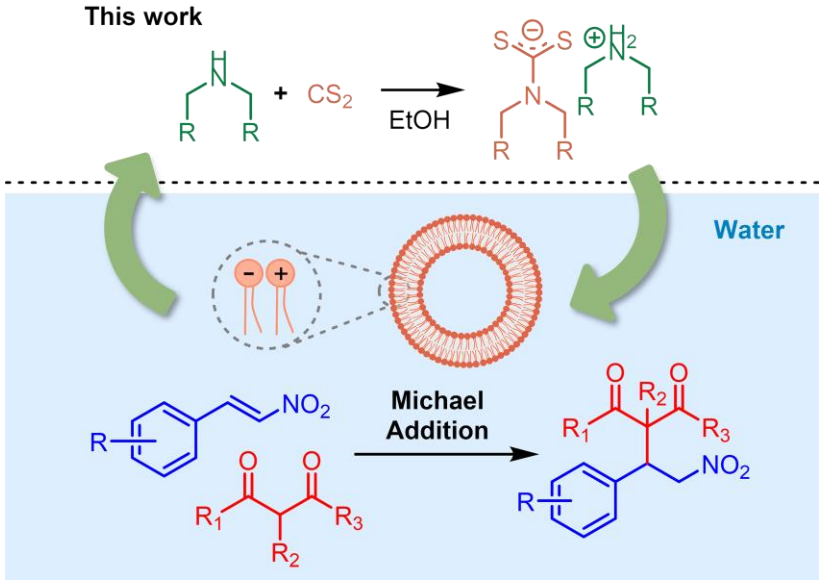


Figure 1. Chemical reactions in nanoreactor of (a) micellar system, (b) vesicular system

The exploration of catalysis using double-chain amphiphiles, typically found in vesicles or liposomes, has been limited compared to the micelles (**Figure 1b**). For instance, the Ugi[34] and Passerini[35] reaction was successfully conducted in the presence of cationic vesicles without additional catalysts. Similarly, there were few reports on the combination of vesicles and catalysts for performing chemical synthesis. Notably, the asymmetric transfer hydrogenation (ATH) reaction was carried out with chiral amphiphiles alongside a rhodium dimer catalyst.[36] Li's group developed amphiphilic catalysts composed of long alkyl chains of the ammonium salts for the cross-aldol reaction.[37] The head group catalyzes the reaction as an enamine catalyst, while the long alkyl chain forms the vesicular system and acts as nanoreactors. Finally, Liu's group utilized CO_2 to trigger the formation of the vesicular nanoreactors.[38] They employed a proline-based amphiphile that forms vesicles under weak acidic bicarbonate solution generated by compression of CO_2 gas. This approach enabled the vesicular nanoreactor to catalyze an aldol reaction with high selectivity.

Dithiocarbamate (DTC) salts can be conveniently synthesized by condensation between secondary amine and carbon disulfide in the presence of a base.[39] They are widely used in several applications, such as chemical intermediates for active pharmaceutical ingredients[40], bioactive compounds[41], synthesis of carbohydrates[42-44], and as chelating ligands for the environmental treatment of heavy metals.[45] Additionally, Jaeger's group reported the formation of an anionic vesicle made from potassium *N*,*N*-didodecyldithiocarbamate. However, the application of this dithiocarbamate vesicle has never been examined. In this study, we hypothesized that a simple one-step condensation between two equivalents of long-chain secondary amine with carbon disulfide could yield the *N*,*N*-dialkylammonium *N*,*N*-dialkyldithiocarbamate (AmDTC) (**Scheme 1**). The AmDTC could be considered a salt-free CatAnionic amphiphile due to its unique chemical structure, which combines both double-chain cationic and double-chain anionic amphiphiles

without the presence of side product-salt. The dispersion of the AmDTC in water can lead to the spontaneous formation of CatAnionic vesicles. We next examine the AmDTC CatAnionic vesicle to serve as the nanoreactor for the Michael addition of nitroolefins as a model reaction. Finally, the reuseability and chemical recycling of AmDTC amphiphiles will be investigated.

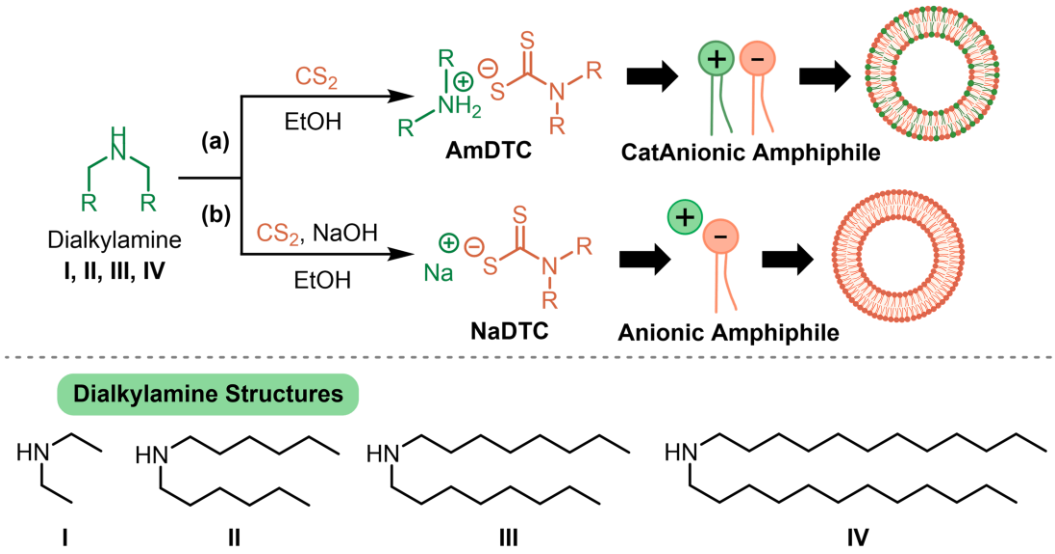


Scheme 1. Synthesis and chemical recyclability of dithiocarbamate vesicular nanoreactor

Results and Discussion

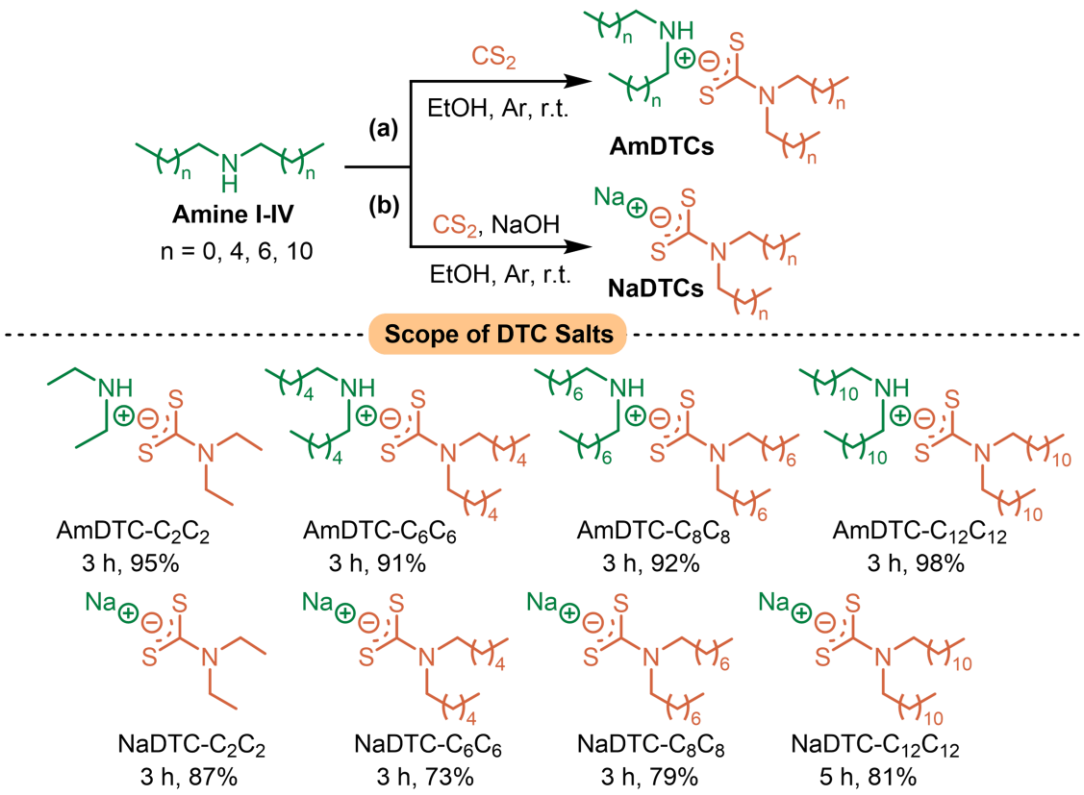
Preparation of Dialkyldithiocarbamate Amphiphiles

Dialkyldithiocarbamate (DTC) salts can be prepared in high yields through a straightforward one-step procedure. First, the CatAnionic amphiphile of *N*,*N*-dialkylammonium *N*,*N*-dialkyldithiocarbamates (AmDTC) was synthesized using two equivalents of a secondary amine **I**-**IV** and one equivalent of CS_2, without the additional base. The first equivalent of amine **I**-**IV** serves as a nucleophile for addition to the CS_2, while the second equivalent of amine serves as a base. (**Scheme 2a**). Next, the synthesis of anionic amphiphile of sodium *N*,*N*-dialkyldithiocarbamates (NaDTC) was carried out employing sodium hydroxide as a base (**Scheme 2b**).



Scheme 2. Synthesis of; (a) AmDTC amphiphile, (b) NaDTC amphiphile

The condensation of CS_2 with secondary amines containing hydrocarbon chains of diethyl, dihexyl, dioctyl, and didodecyl groups proceeds smoothly over a period of 3–5 hours at room temperature, as shown in **Scheme 3**. After the reactions have finished, the mixture is allowed to crystallize or precipitate for purification. This process results in the desired AmDTC and NaDTC as a white solid. The AmDTC yields ranged from 91–98% (**AmDTC-C_2C_2** = 95%, **AmDTC-C_6C_6** = 91%, **AmDTC-C_8C_8** = 92%, **AmDTC-$C_{12}C_{12}$** = 98%), while the NaDTC yields ranged from 73–87% (**NaDTC-C_2C_2** = 87%, **NaDTC-C_6C_6** = 73%, **NaDTC-C_8C_8** = 79%, **NaDTC-$C_{12}C_{12}$** = 81%).



Scheme 3. Synthesis of AmDTC and NaDTC with different hydrocarbon chain lengths

Characterization of Vesicular Nanoreactor from Dithiocarbamate Amphiphiles

Dynamic light scattering (DLS) measurements revealed distinct variations in particle diameter of DTC amphiphiles, ranging from 295 to 397 nm (**Figure 2**). The NaDTC amphiphiles (295–344 nm) exhibited smaller particle sizes compared to the AmDTC amphiphiles (347–397 nm). This was because the AmDTCs form CatAnionic vesicles containing both cationic amphiphiles (dialkylammonium cations) and anionic amphiphiles (dithiocarbamate anions) within the hydrophobic layer, leading to a larger size than NaDTC amphiphiles. Additionally, DTC amphiphiles with longer hydrocarbon chain lengths, such as **AmDTC-$C_{12}C_{12}$**, dispersed in water with larger diameter size (397 nm), while those with shorter hydrocarbon chains, like **AmDTC-C_6C_6** (347 nm) and **AmDTC-C_8C_8** (357 nm), showed smaller diameters. These results aligned with the correlation between hydrocarbon chain length and particle size. Moreover, the polydispersity index (PDI) value was below 0.3, indicating a homogeneous population of particles.[46] These findings demonstrate that DTC amphiphiles can disperse in water of various sizes without precipitation.

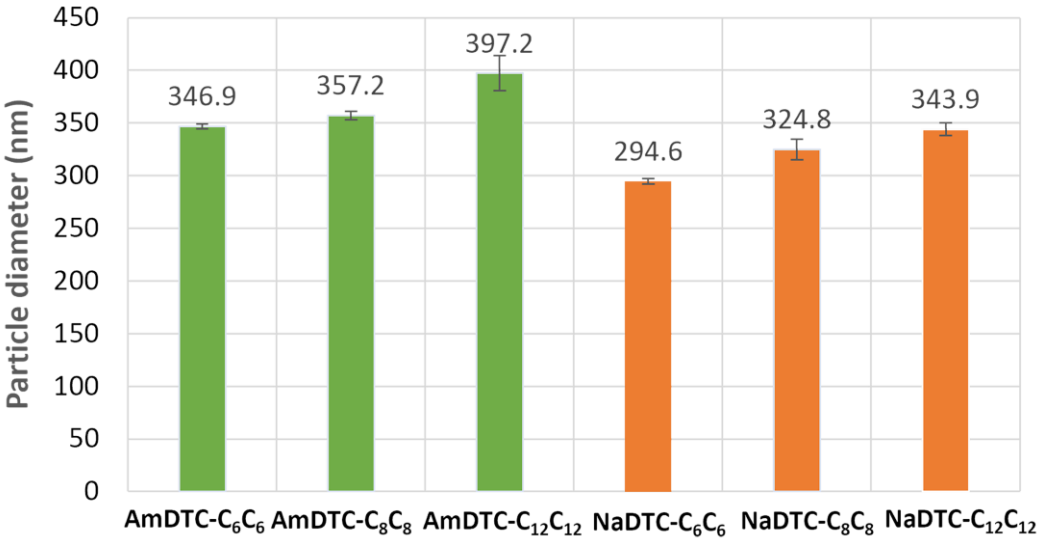


Figure 2. Particle diameter of DTC amphiphiles in water

Transmission electron microscopy (TEM) was employed to investigate the morphology of the DTC vesicles. As depicted in **Figure 3**, the TEM images corroborate the spherical shape of the DTC vesicles, which exhibit diameters ranging from approximately 143 to 294 nm.

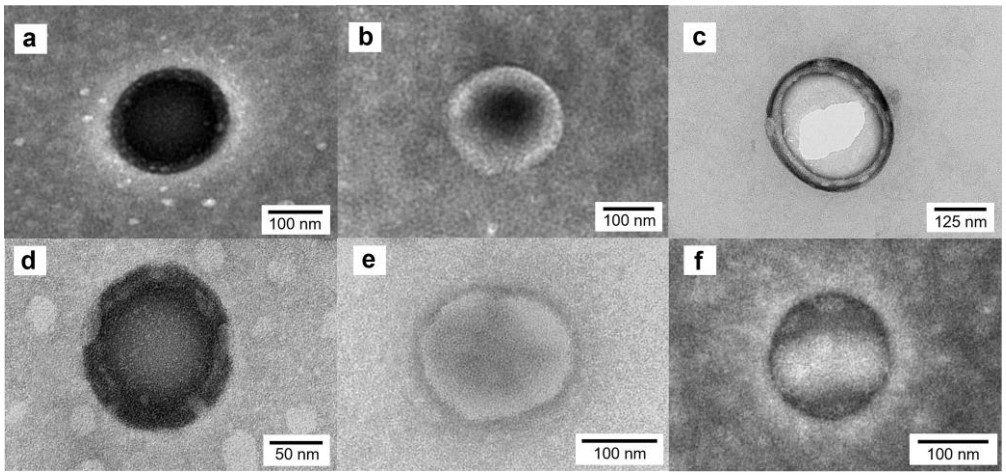


Figure 3. TEM micrographs for morphology investigation of (a) **AmDTC-C_6C_6**, (b) **AmDTC-C_8C_8**, (c) **AmDTC-$C_{12}C_{12}$**, (d) **NaDTC-C_6C_6**, (e) **NaDTC-C_8C_8**, and (f) **NaDTC-$C_{12}C_{12}$**

The stability of the DTC amphiphiles in an aqueous environment was evaluated by zeta potential measurements. Typically, a high zeta potential value, either above +30 mV or below –30 mV, indicates a stable dispersion of particles, suggesting resistance to self-aggregation.[47, 48] Conversely, a decrease in zeta potential implies that the particles could attract to each other, potentially leading to coagulation by overcoming repulsion forces. Results from the zeta potential measurements revealed that the DTC particles exhibited a negative surface potential, ranging from –15.8 mV to –77.0 mV (**Figure 4**), a characteristic attributed to their anionic amphiphilic nature. However, it is noteworthy that the zeta potential values of **AmDTC-C_6C_6** (–15.8 mV) and

AmDTC-C_8C_8 (–22.3 mV) exceed the conventional stability threshold (above –30 mV). This observation suggests lower stability, potentially influenced by the electrostatic interactions between cationic and anionic amphiphile, thereby impeding the overall stability of the vesicles. A comparison between NaDTCs and AmDTCs with the same hydrocarbon chain length showed notable differences in zeta potential values. This difference was attributed to the association of NaDTC in water as an anionic double-chain amphiphile, leading to a large negative value on its surface, ranging from –59.3 to –77.0 mV. In contrast, AmDTCs were observed to associate as a CatAnionic amphiphile, displaying characteristics of both cationic and anionic amphiphile on its surface, resulting in smaller negative values ranging from –15.8 to –40.6 mV.

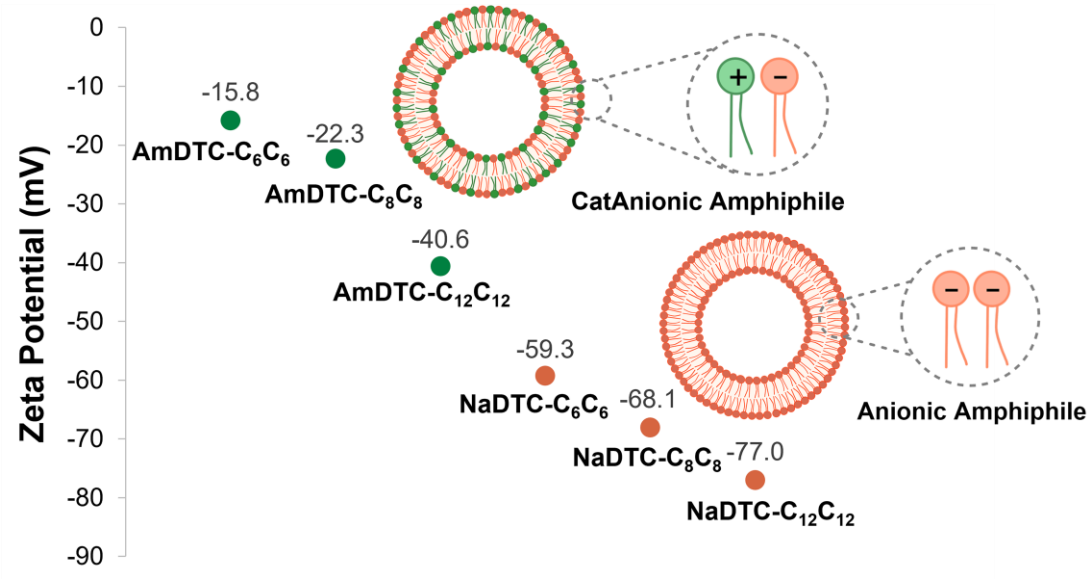


Figure 4. Zeta potentials of DTC amphiphiles in water

The critical vesicle concentration (CVC) of the DTC amphiphile was examined by fluorescence spectroscopy using Nile Red (NR) as a fluorescence probe. The first inflection point on the plot of fluorescence intensity against log vesicle concentrations was used to determine the CVC values. From the results, the calculated CVC value of **AmDTC-$C_{12}C_{12}$** was found to be 2.19 mg/mL (0.22 %w/w, 2.8 mM). The remarkable stability of the DTC amphiphiles, especially those variants with long hydrocarbon chain lengths, has prompted further investigation into their potential roles as vesicular nanoreactors in an aqueous medium.

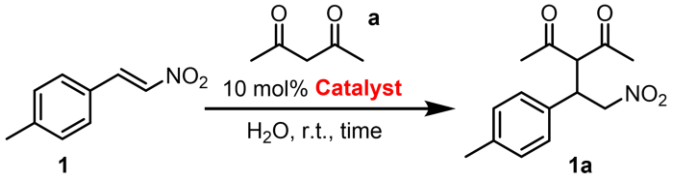
Evaluation of the Catalytic Activity of Vesicular Nanoreactor from Dithiocarbamate

Michael addition stands out as one of the most efficient transformations commonly utilized in the synthesis of bioactive compounds.[49, 50] This reaction can be catalyzed by a range of organocatalysts[51], especially hydrogen-bonding activation of thiourea-based and squaramide-based organocatalysts in aqueous medium.[52, 53] However, the multi-step synthesis of these catalysts increases waste and resource consumption. The Michael addition of *trans*-4-methyl-β-nitrostyrene (**1**) with 2,4-pentadione (**a**) was selected as a model reaction to assess the

catalytic activity of DTC amphiphiles. The reaction was carried out in an aqueous medium at room temperature, using 10 mol% of DTC amphiphile, and the results are summarized in **Table 1**.

For the NaDTC as anionic amphiphiles, **NaDTC-C_2C_2** possesses the shortest hydrocarbon chain length and does not form vesicles in water. As a result, the reaction between the Michael donor and acceptor proceeded heterogeneously and reached completion over 20 hours, yielding 51% for the Michael adduct **1a** (**Table 1**, entry 1). Additionally, **NaDTC-C_6C_6** and **NaDTC-C_8C_8**, with longer hydrocarbon chains, served as effective catalysts, completing the reaction in 8.5 hours, and yielding product **1a** in 65% and 69%, respectively (entries 2 and 3). **NaDTC-$C_{12}C_{12}$**, featuring the longest hydrocarbon chain length in the NaDTC amphiphiles, expedited the reaction which was completed in 7.5 hours with a 73% yield (entry 4). Introducing a larger potassium cation, **KDTC-$C_{12}C_{12}$** exhibited similar catalytic activity to that of **NaDTC-$C_{12}C_{12}$** with a 65% yield (entry 5). Increasing the hydrophobicity of DTC by extending the chain length enables the formation of DTCs as vesicular nanoreactors. This enhancement in hydrophobicity contributes to increased homogeneity in the reaction and accelerates its progression. However, it is noteworthy that the use of NaDTCs and KDTC as catalysts led to the formation of an unidentified side product, resulting in a reduction in the yields compared to AmDTC.

Table 1. Michael addition of *trans*-4-methyl-β-nitrostyrene (**1**) catalyzed by DTCs



Entry[a]	Catalyst	Time (h)	Conversion[b] (%)	Yield[c] (%)
1	NaDTC-C_2C_2	20	100	51
2	NaDTC-C_6C_6	8.5	100	65
3	NaDTC-C_8C_8	8.5	100	69
4	NaDTC-$C_{12}C_{12}$	7.5	100	73
5	KDTC-$C_{12}C_{12}$	7.5	100	65
6	AmDTC-C_2C_2	22	100	53
7	AmDTC-C_6C_6	8	100	69
8	AmDTC-C_8C_8	8	100	71
9	**AmDTC-$C_{12}C_{12}$**	**7**	**100**	**90**
10	no catalyst	24	0	0

[a]Standard conditions: Catalyst (10 mol%), H_2O 1.5 mL, r.t. (27–30 °C), 3 h then a Michael acceptor **1** (0.30 mmol), Michael donor **a** (1.2 equiv.). [b]Conversion was determined based on ^{1}H NMR analysis of the reaction mixture. [c]Isolated yields.

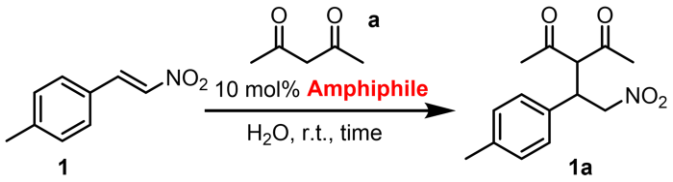
Within the AmDTC as CatAnionic amphiphiles, the catalyst **AmDTC-C_2C_2**, having the shortest hydrocarbon chain length, was employed in the reaction. Similar to **NaDTC-C_2C_2**, it did not form a vesicular system, thus the reaction also proceeded heterogeneously. The reaction extended over 22 hours, yielding 53% of Michael adduct **1a** (entry 6). **AmDTC-C_6C_6** and **AmDTC-C_8C_8** similarly showed catalytic efficacy, completing the reaction in 8 hours and producing the desired product **1a** in similar yields of 69% and 71% (entries 7 and 8). However, these yields were surpassed by **AmDTC-$C_{12}C_{12}$**, which exhibited outstanding catalytic ability for the Michael addition. The reaction with the **AmDTC-$C_{12}C_{12}$** was completed within 7 hours, affording product **1a** a remarkable 90% yield (entry 9). The results collectively indicate that the DTC amphiphiles can effectively catalyze the reaction, and their hydrophobic nature enables the creation of a vesicular system, thereby enhancing the reaction rate. Furthermore, the CatAnionic AmDTC did not yield the unidentified side product observed in the anionic NaDTC amphiphiles, indicating a higher level of selectivity of AmDTC amphiphiles.

On the basis of these findings, we postulated that the efficiency resulted from the hydrophobicity of the long-chain hydrocarbon moieties of the DTC amphiphiles, which yield vesicle formation during the reaction. The nitroolefins **1** and 1,3-dicarbonyl **a** were encapsulated inside the hydrophobic pocket, resulting in a significant increase in the relative concentration of the substrates in the vesicles and the ability to accelerate the reaction rate. Furthermore, the cation was also responsible for the efficiency since the dialkylammonium cation provided a higher yield of Michael adduct **1a** in comparison to sodium and potassium ions. Thus, the CatAnionic **AmDTC-$C_{12}C_{12}$** was chosen as an optimum vesicular nanoreactor in this study.

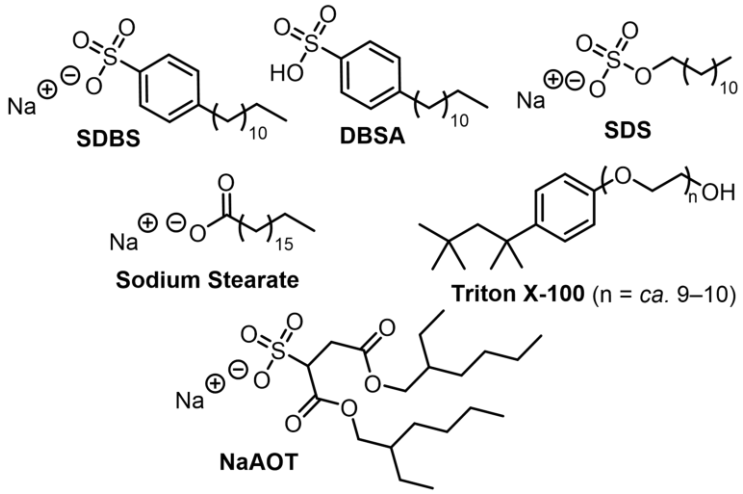
The Influence of Various Amphiphiles on the Efficiency of Michael Addition

We hypothesized that the **AmDTC-$C_{12}C_{12}$** was engaged in the catalysis of the Michael addition in addition to serving as a hydrophobic vesicular nanoreactor. To gain insight into the dual functionality of **AmDTC-$C_{12}C_{12}$** vesicular catalyst, we investigated various amphiphiles that form vesicles and micelles. A variety of amphiphiles were examined in this study, including single- and double-chain amphiphiles (**Table 2**). For use as a micellar model, four anionic and one non-ionic single-chain amphiphile were chosen: sodium dodecylbenzenesulfonate (SDBS), sodium dodecylsulfate (SDS), sodium stearate, dodecylbenzenesulfonic acid (DBSA), and Triton X-100. Another anionic double-chain amphiphile that was used was sodium bis(2-ethylhexyl) sulfosuccinate (NaAOT), which transformed into a vesicle when dispersed in water.

Table 2. The influence of various amphiphiles on Michael Addition



Entry[a]	Amphiphile	Time (h)	Conversion[b] (%)	Yield[c] (%)
1	**AmDTC-$C_{12}C_{12}$**	**7**	**100**	**90**
2	SDBS	48	0	0
3	DBSA	48	0	0
4	SDS	48	0	0
5	Triton X-100	48	0	0
6	Sodium stearate	96	75	32
7	NaAOT	48	0	0
8	SDS + NaDTC-C_2C_2	12	100	44
9	Triton X-100 + NaDTC-C_2C_2	12	100	45
10	NaAOT + NaDTC-C_2C_2	24	100	40



[a]Standard conditions: Michael acceptor **1** (0.30 mmol), a Michael donor **a** (1.2 equiv.), amphiphile (10 mol%; conc. above CMC or CVC), H_2O 1.5 mL, r.t. (27–30 °C). [b]Conversion was determined based on ^1H NMR analysis of the reaction mixture. [c]Isolated yields.

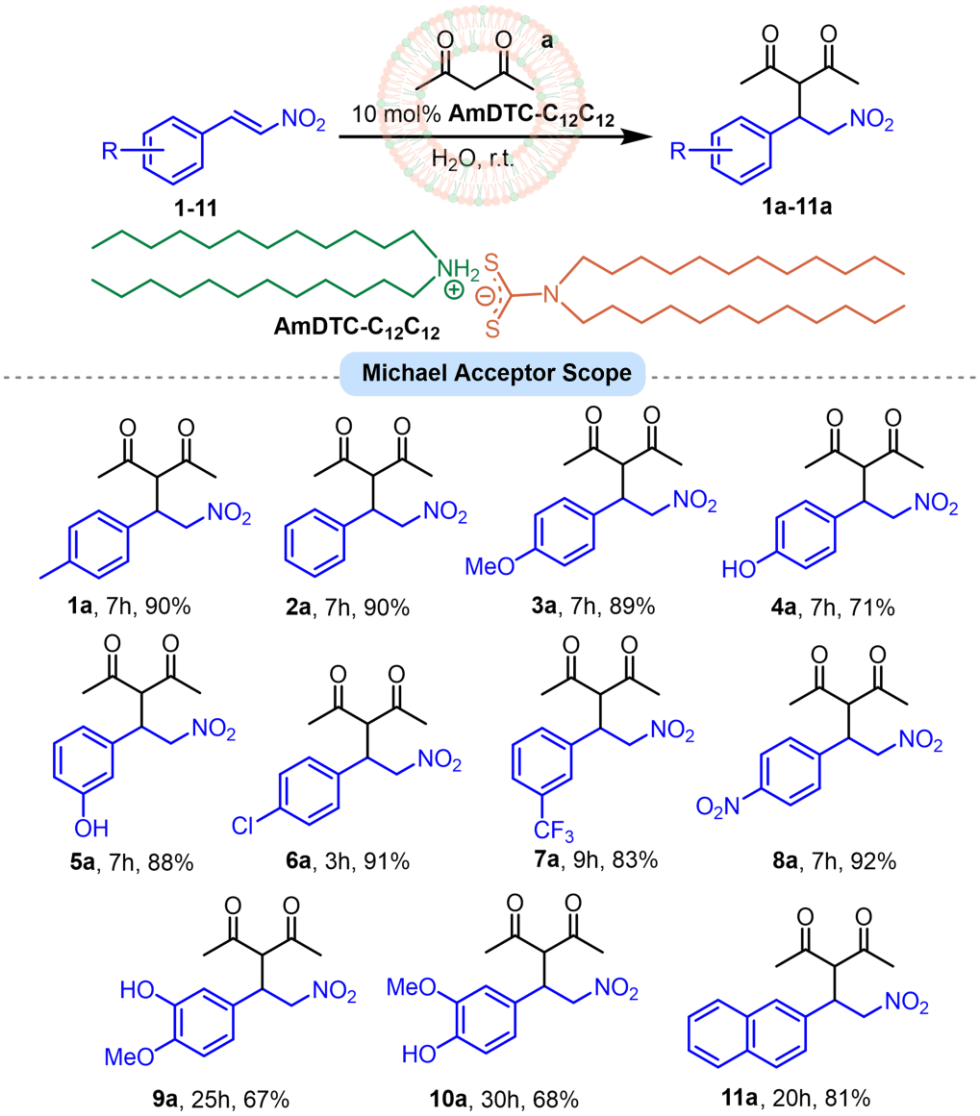
In the case of single-chain amphiphiles, neither SDBS, SDS, DBSA, nor Triton X-100 were able to accelerate the Michael addition, even after the prolonged reaction time of 48 hours (**Table 2**, entries 2–5). Sodium stearate, however, produced the desired Michael adduct **1a** in

75% conversion and product in low yield (32%) after 96 hours (entry 6). The partial conversion may occur by the catalysis of weak basic sodium carboxylate. Interestingly, the NaAOT vesicle gave a result similar to the micellar systems and did not provide the Michael adduct even after 48 hours (entry 7). According to these results, the amphiphilic feature alone—whether in the form of micelles or vesicles—is insufficient to accelerate the reaction to completion. Next, we hypothesized adding **NaDTC-C_2C_2** into the amphiphiles should increase the conversion since the reaction medium would have both catalyst and amphiphile. In addition, three further combinations of **NaDTC-C_2C_2** + SDS (anionic micellar system; entry 8), **NaDTC-C_2C_2** + Triton X-100 (non-ionic micellar system; entry 9), and **NaDTC-C_2C_2** + NaAOT (anionic vesicular system; entry 10) were examined. A combination of **NaDTC-C_2C_2** + SDS and **NaDTC-C_2C_2** + Triton X-100 resulted in faster completion, reaching only 12 hours, with a 44% and 45% yield of **1a**, respectively (entries 8 and 9). Similarly, a combination of **NaDTC-C_2C_2** + NaAOT resulted in completion within 24 hours, with only 40% yield of **1a** (entry 10). It should be mentioned that despite a full consumption of nitroolefins **1** in entries 8–10, the yields of Michael adduct **1a** remained low, as shown by the presence of unidentified impurities observed in the ^{1}H NMR of the crude mixture. To conclude, the yields of the Michael adduct **1a** in all cases remained inferior compared to when **AmDTC-$C_{12}C_{12}$** was used alone as a vesicular nanoreactor, yielding 90% of **1a** (entry 1). These results reveal the importance of the presence of the dithiocarbamate moiety in the amphiphile for catalyzing the reaction, not only for hydration with the water medium during vesicle formation. Therefore, the **AmDTC-$C_{12}C_{12}$**, which catalyzes the reaction and serves as a vesicle, was chosen as the optimal catalyst for the following studies.

Substrate Scope of Michael Acceptor with AmDTC-$C_{12}C_{12}$ Vesicular Nanoreactor

Having the optimal conditions in hand, 10 mol% (14.7 mg/mL or 1.53 %w/w or 20 mM; the concentration was higher than the CVC) of **AmDTC-$C_{12}C_{12}$** was employed as a vesicular nanoreactor for the Michael addition with various substrates. The investigation focused on substituted β-nitrostyrenes (Michael acceptors) **1**–**11**, featuring either electron-withdrawing or electron-donating substituents on the aromatic ring, and 2,4-pentanedione (**a**) as the Michael donor in an aqueous medium. The results are summarized in **Scheme 4**. The Michael additions were successfully conducted with 10 mol% **AmDTC-$C_{12}C_{12}$** in water at room temperature, producing the desired Michael adducts **1a**–**11a** ranging from 67% to 92% yields. The reactivity of β-nitrostyrene was influenced by the substituent groups on the aromatic ring. The Michael reaction with β-nitrostyrene having methyl, methoxy, and hydroxy groups (electron-donating substituents) in the *para*-position of the aromatic ring was completed within 7 hours, resulting in desired Michael adducts with yields ranging from 71% to 90% (**1a**, **3a**, **4a**). Meanwhile, the β-nitrostyrene with a hydroxy group at the *meta*-position provided a comparable yield of 90% (**5a**). Subsequently, the *para*-chloro substituted β-nitrostyrene **6** demonstrated good reactivity, as expected, with a yield of the Michael adduct **6a** of 91%. This was followed by the reaction with the β-nitrostyrene substituted with a trifluoromethyl moiety at the *meta*-position, which produced the Michael adduct **7a** in 83% yield, albeit with a slightly longer reaction time of 9 hours. The presence of an electron-withdrawing group, such as the *para*-nitro group, positively influenced the reaction, which led to a high yield of 92% for Michael adduct **8a**. In contrast, highly

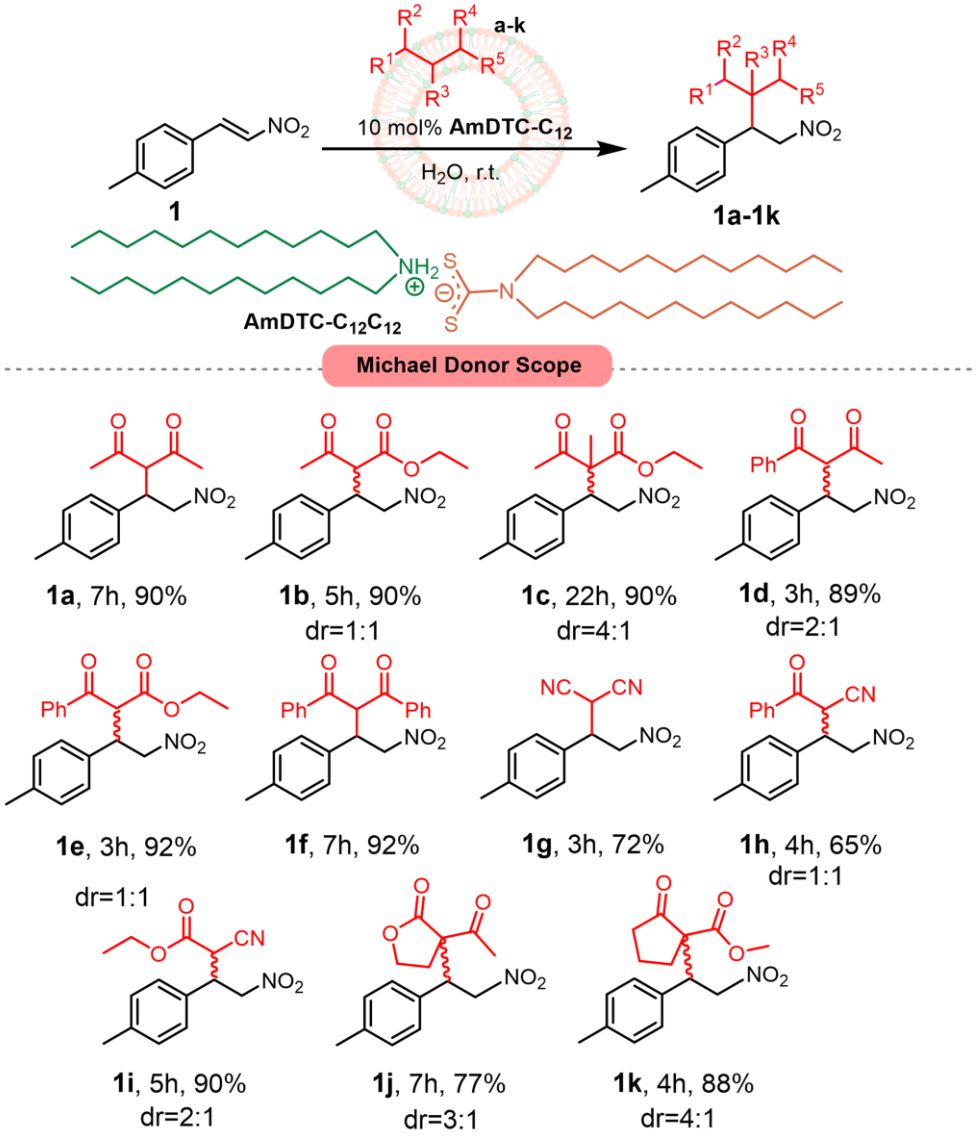
electron-rich β-nitrostyrenes, equipped with two electron-donating groups on the aromatic ring, exhibited lower reactivity. They produced the Michael adducts **9a** and **10a** at 67% (25 h) and 68% (30 h), respectively. Finally, the Michael addition of *trans*-2-naphthalene-β-nitrostyrene **11** produced the desired product **11a** after 20 hours with a yield of 81%. Regarding the scope of β-nitrostyrene, the reported conditions here were generally applicable to β-nitrostyrene equipped with both electron-donating and withdrawing group, except for the highly electron-rich β-nitrostyrenes (**9**–**11**) that required longer reaction times and obtained the Michael adducts in lower yields. The slower reaction rate is explained by the lower reactivities of alkenes conjugated to the electron-rich aromatic ring.



Scheme 4. The substrate scope of Michael acceptors. Standard conditions: **AmDTC-$C_{12}C_{12}$** (10 mol%), H_2O 1.5 mL, r.t. (27–30 °C), 3 h then Michael acceptors (0.27–0.35 mmol) and 2,4-pentanedione (1.2 equiv.).

Substrate Scope of Michael Donor with AmDTC-$C_{12}C_{12}$ Vesicular Nanoreactor

The effectiveness of employing various β-nitrostyrenes as Michael acceptors was established, prompting an exploration of the scope of 1,3-dicarbonyls and malononitrile as Michael donors (**a**–**k**). As illustrated in **Scheme 5**, Michael additions of six Michael donors, *i.e.*, 2,4-pentanedione (**a**), ethyl 3-oxobutanoate (**b**), 1-phenylbutane-1,3-dione (**d**), ethyl 3-oxo-3-phenylpropanoate (**e**), 1,3-diphenylpropane-1,3-dione (**f**), and ethyl 2-cyanoacetate (**i**) provided the Michael adducts (**1a**, **1b**, **1d**, **1e**, **1f**, and **1i**) in high yields ranging from 89–92% within 3–7 hours.



Scheme 5. The substrate scope of Michael acceptors. Standard conditions: **AmDTC-$C_{12}C_{12}$** (10 mol%), H_2O 1.5 mL, r.t. (27–30 °C), 3 h then Michael acceptor **1** (0.30 mmol), Michael donors (1.2 equiv.). Isolated yields after column chromatography and the diastereoselectivities (dr) were determined by ^1H NMR integration.

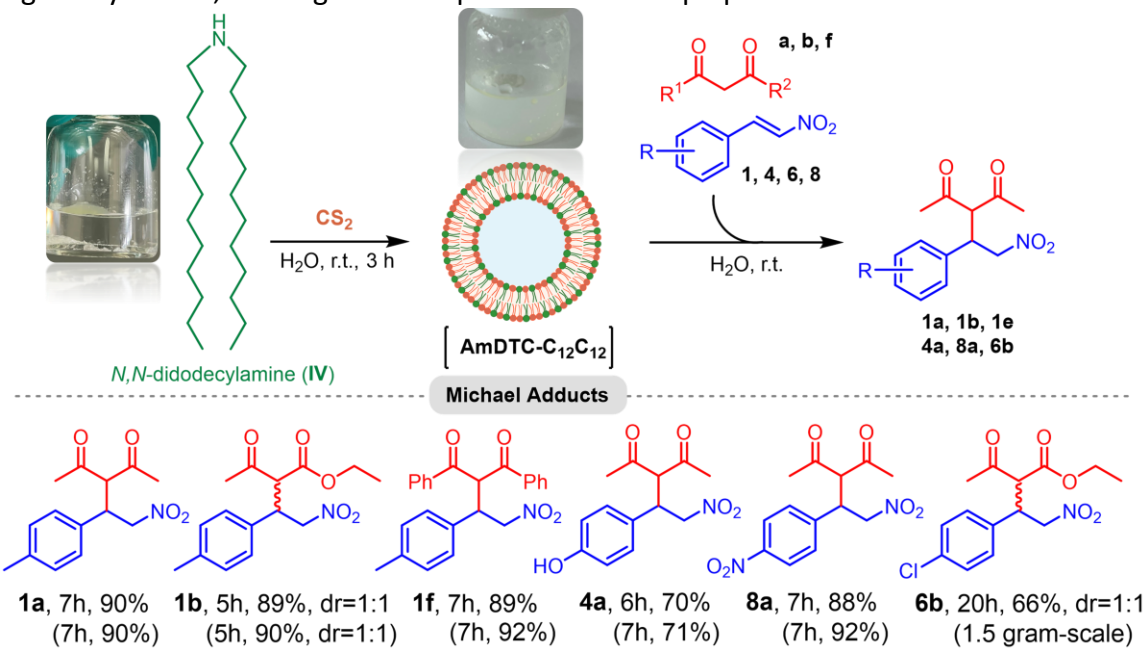
Low to moderate diastereoselectivities were observed in Michael adducts **1b**–**1e** and **1h**–**1k**, with ratios ranging from 1:1 to 4:1. The presence of large or bulky groups in the Michael donor can obstruct the accessibility of the enolate nucleophile to the electrophilic center of β-nitrostyrene, diminishing the efficiency of the reaction. For instance, the Michael adduct **1c** was afforded in 90% (dr= 4:1) but required an extended reaction time of 22 hours for completion. The utilization of malononitrile (**g**) and benzoylacetonitrile (**h**) as Michael donors resulted in slight decreases in yield for the corresponding addition products **1g** (72%) and **1h** (65%, dr= 1:1) due to the formation of undesired side products. The Michael addition with the reactive cyclic Michael donors, such as α-acetylbutyrolactone (**j**) and methyl-2-oxocyclopentane carboxylate (**k**), provided good yields and moderate diastereoselectivities for the products **1j** (77%, dr= 3:1, 7 h) and **1k** (88%, dr= 4:1, 4 h).

One-pot Michael Addition by *In Situ* Generation of AmDTC-$C_{12}C_{12}$ Vesicle

Our process for the Michael addition generally consists of two steps: 1) The synthesis of **AmDTC-$C_{12}C_{12}$** by condensation between secondary amine and CS_2 in ethanol. After 3 hours, the reaction mixture was concentrated and underwent precipitation using acetone and water. 2) Preparation of the vesicle by treatment of the solid **AmDTC-$C_{12}C_{12}$** with isopropanol and water. The Michael donors and acceptors were added after removing isopropanol from the reaction mixture. Despite good yields of the Michael adducts, we sought to investigate the *in situ* generation of **AmDTC-$C_{12}C_{12}$** for the Michael addition**.** The concept of *in situ* synthesis of amphiphile for vesicle formation has been previously demonstrated. For example, Devaraj and co-workers employed copper-catalyzed azide−alkyne cycloaddition (CuAAC), Click chemistry, for the *in situ* synthesis of phospholipid.[54, 55] In our work, the *in situ* generation of **AmDTC-$C_{12}C_{12}$** could simplify the synthetic procedure in a one-pot manner (pot economy)[56], lower the amount of time needed to prepare and purify **AmDTC-$C_{12}C_{12}$** (time economy)[57], and eliminate the use of all organic solvents, *i.e.*, ethanol, isopropanol, and acetone. Following the protocol outlined, *N*,*N*-didodecylamine and CS_2 were added to the water. This resulted in a heterogeneous mixture of solid *N*,*N*-didodecylamine at the bottom of the vessel, and CS_2 on top of the water layer. After vigorously stirring the mixture for 3 hours, the reaction mixture turned into a cloudy suspension. A small portion of the reaction mixture was collected, and the formation of the **AmDTC-$C_{12}C_{12}$** was verified by ^{1}H NMR analysis, which confirmed a total conversion of *N*,*N*-didodecylamine to **AmDTC-$C_{12}C_{12}$**.

Subsequently, Michael donors and acceptors were added, and the reaction promptly proceeded. Delightfully, the chemical reactivity of Michael donors and acceptors remained consistent with previous results using purified **AmDTC-$C_{12}C_{12}$** (**Schemes 4**, **5**). Five Michael adducts were obtained in comparable yields and diastereoselectivity by using *in situ* generation of **AmDTC-$C_{12}C_{12}$** vesicle (10 mol%) as follows: **1a** (90%), **1b** (89%, dr= 1:1), **1f** (89%), **4a** (70%), and **8a** (88%) (**Scheme 6**). To the best of our knowledge, this is the first report on the *in situ* generation of amphiphile that was consequently employed as nanoreactors in chemical synthesis. A preparative-scale synthesis of Michael adduct **6b** *via in situ* generation of **AmDTC-$C_{12}C_{12}$** vesicle (10 mol%) was demonstrated in a 1.5 gram-scale of the 4-chloro-β-nitrostyrene (**6**). Following chromatographic purification, the desired product **6b** was afforded in 1.71 grams (66%, dr= 1:1). These results showed that the developed procedure is straightforward and suitable for

synthesis on a preparative scale. Notably, only water was required as a reaction medium/solvent during the synthesis, starting from the production of amphiphile.



Scheme 6. One-pot Michael addition by *in situ* generation of **AmDTC-$C_{12}C_{12}$** vesicle (10 mol%) and yields in parentheses are from the protocol using purified **AmDTC-$C_{12}C_{12}$**

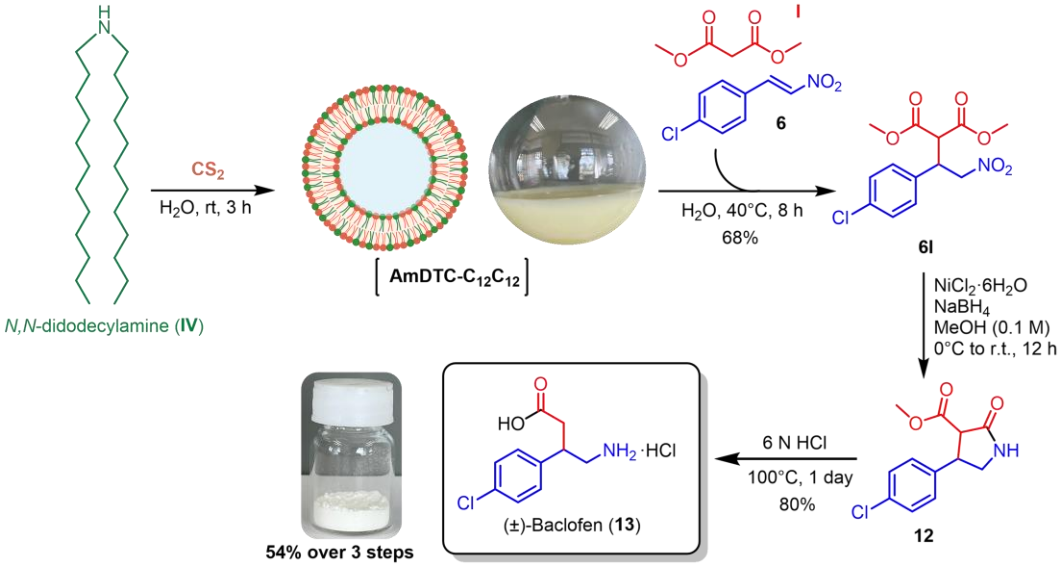
We acknowledged that CS_2 is recognized as a hazardous solvent for chemical synthesis due to its volatility and flammability.[58] After careful consideration, we deemed that the risk from CS_2 was minimal and acceptable in this work. Our procedure used CS_2 in a stoichiometric fashion, not as a solvent, and only required 10 mol% of **AmDTC-$C_{12}C_{12}$** for each transformation. Moreover, the *in situ* generation of **AmDTC-$C_{12}C_{12}$** facilitated the use of CS_2 in small quantities since it did not require a prior production of **AmDTC-$C_{12}C_{12}$** in large amounts.

Synthesis of Baclofen in Preparative-scale *via* One-pot Michael Addition using AmDTC-$C_{12}C_{12}$

The Michael adducts serve as valuable intermediates in the synthesis of active pharmaceutical ingredients. GABA analogs, exemplified by γ-aminobutyric acid, play a pivotal role as inhibitory neurotransmitters within the central nervous system (CNS) and find widespread applications, notably as antidepressants, anticonvulsants, and antispasmodics.[52] Baclofen is a GABA analog that is used therapeutically to treat muscle spasms, especially those caused by disorders like multiple sclerosis or spinal cord damage.[59] Baclofen is commercialized in its racemic form[60], thus serving as a suitable target for our method. Herein, we applied the vesicular nanoreactor of **AmDTC-$C_{12}C_{12}$** as an organocatalyst to synthesize (±)-baclofen (**Scheme 7**).

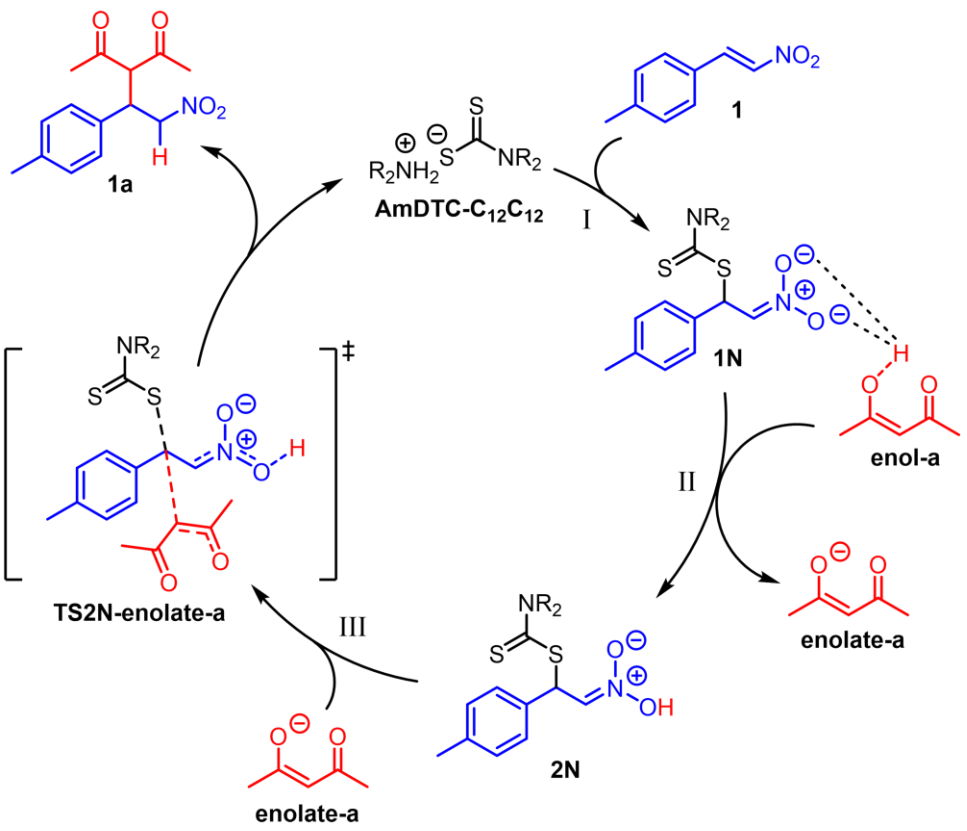
The one-pot Michael addition was carried out using 4-chloro-β-nitrostyrene (**6**) and dimethyl malonate (**l**) as precursors to afford Michael adduct **6l**. Due to the low reactivity of dimethyl malonate (pKa = 13), the reaction temperature was adjusted to 40 °C to afford the optimum yield. Under these conditions, a grams-scale synthesis of (±)-baclofen was carried out

with 1.5 grams of 4-chloro-β-nitrostyrene (**6**). The corresponding Michael adduct **6l** was obtained in 68% yield after chromatographic purification. With the aid of a nickel boride catalyst, the nitro group on Michael adduct **6l** was reduced to the amine and followed by cascade lactonization. The nickel boride was generated by the treatment of nickel chloride ($NiCl_2 \cdot 6H_2O$) with sodium borohydride ($NaBH_4$). This process resulted in the generation of lactone **12**. Subsequent decarboxylation and hydrolysis were carried out using 6 N of hydrochloric acid (HCl) without prior purification, yielding the (±)-baclofen hydrochloride **13** as the final product in 80% (2-step yield). Overall, the synthesis was executed in 3 steps, starting from 4-chloro-β-nitrostyrene (**6**), and required one chromatographic purification of the Michael adduct **6l**. This three-step synthesis produced an overall yield of 54%.



Scheme 7. Preparative-scale synthesis of (±)-baclofen **13**

Based on these findings, a working mechanism for the Michael addition using **AmDTC-$C_{12}C_{12}$** as the vesicular nanoreactor is proposed (**Scheme 8**). The **AmDTC-$C_{12}C_{12}$** not only provides hydrophobicity from the didodecyl hydrocarbon chains but is also involved in catalysis at the dithiocarbamate (DTC) group. The DTC provides dual functions as a hydrophilic head for vesicle formation and a reactive site for catalysis. Delving into the mechanism, the first step involves the nucleophilic addition of **AmDTC-$C_{12}C_{12}$** to the nitroolefin (**1**), which results in the generation of the adduct **1N** (**step I**). This addition likely takes place at the interface between the vesicle's surface and the hydrophobic bilayer. Next, a protonation of **1N** by **enol-a** yields nitronic acid **2N** and **enolate-a** (**step II**). Simultaneous substitution of **2N** by the **enolate-a** at the α-carbon and proton transfer at the β-carbon, as depicted in the transition state **TS2N-enolate-a**, culminating in the formation of the desired Michael adduct **1a** and releasing the **AmDTC-$C_{12}C_{12}$** for the next catalytic cycle (**steps III**).



Scheme 8. The working mechanism of Michael addition in water using **AmDTC-$C_{12}C_{12}$**

Reusability of the AmDTC-$C_{12}C_{12}$ Vesicular Nanoreactor

Next, the reusability of the **AmDTC-$C_{12}C_{12}$** was examined. We employed a precipitation technique to recover the **AmDTC-$C_{12}C_{12}$** from the reaction mixture. The polarity of the aqueous medium is gradually decreased by adding a water-miscible organic solvent to the solution until the **AmDTC-$C_{12}C_{12}$** precipitates out while the Michael adduct (and other organic materials) continues to dissolve in the reaction mixture. After several attempts, acetonitrile serves best for recovering **AmDTC-$C_{12}C_{12}$**. Once the Michael addition was completed, acetonitrile was added to the reaction mixture in an amount equivalent to about the same volume of water, or until the amount of **AmDTC-$C_{12}C_{12}$** precipitate was no longer increased. After the **AmDTC-$C_{12}C_{12}$** was filtered as a solid, the filtrate underwent additional purification using column chromatography, which produced the Michael adduct (refer to the supplementary information for details). Subsequently, a fresh portion of water was added to the recovered **AmDTC-$C_{12}C_{12}$**, followed by the addition of Michael donor **a** and acceptor **1**, and the reaction was initiated for the next cycle (**Figure 5**).

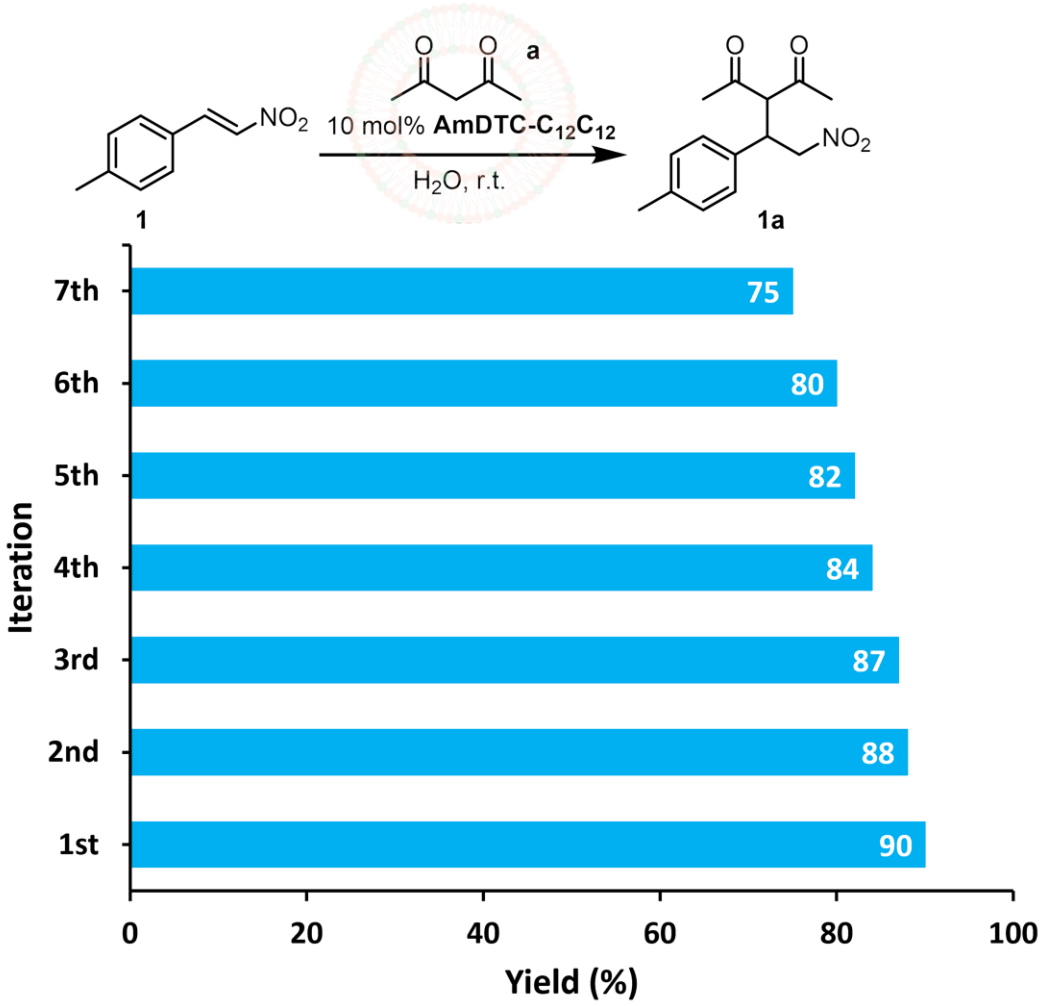


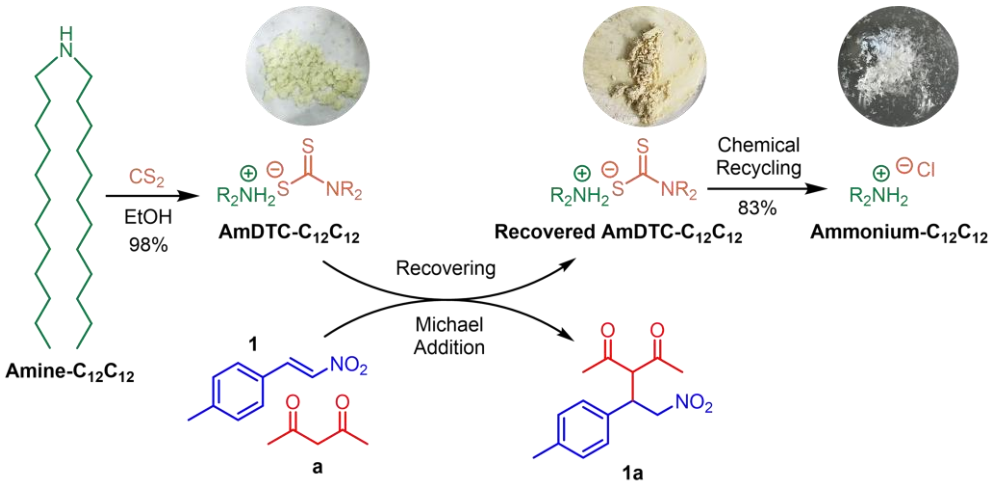
Figure 5. Reusability of the **AmDTC-$C_{12}C_{12}$** vesicular nanoreactor

During the 2nd to the 7th cycles, the Michael additions went smoothly, resulting in full conversion and yielding the desired product consistently. Nevertheless, the yields of Michael adduct **1a** were gradually reduced from 90% (1st cycle), 88% (2nd cycle), 87% (3rd cycle), 84% (4th cycle), 82% (5th cycle), 80% (6th cycle), and 75% (7th cycle). Notably, the solid recovered from the 7th cycle was hardly suspended and precipitated out in water. As a result, when the solid was applied for the 8th cycle, the vesicular formation of **AmDTC-$C_{12}C_{12}$** was limited. By the 8th cycle, an incomplete conversion of Michael acceptor **1** was observed. The deterioration of the yields of Michael adduct **1a** could be caused by a loss of **AmDTC-$C_{12}C_{12}$** during each recovery cycle and probably due to a slow air-oxidation of dithiocarbamate to non-polar thiuram disulfide, which readily precipitated in a water medium, as observed earlier after the 7th cycle recovery.

Chemical Recycling of the AmDTC-$C_{12}C_{12}$

The slow air-oxidation of dithiocarbamate to thiuram disulfide could hamper prolonged storage of **AmDTC-$C_{12}C_{12}$** or require additional precautions to be stored under an inert atmosphere. Furthermore, if a valuable secondary amine is to be used for the generation of DTC,

chemical recycling of the amine becomes a necessary option. This study presents an approach to performing chemical recycling of the **AmDTC-$C_{12}C_{12}$** back to the secondary amine. The chemical recycling of **AmDTC-$C_{12}C_{12}$** is based on decomposing dithiocarbamic acid to the secondary amine and CS_2. The dithiocarbamic acid is promptly generated by an acidic treatment of **AmDTC-$C_{12}C_{12}$**. Following the preliminary optimization (refer to the supplementary information for details), the chemical recycling was carried out as follows: after the recovery of **AmDTC-$C_{12}C_{12}$** by precipitation, the solid was dissolved in ethanol, acidified with a solution of 6 N HCl, and heated to 80 °C. The *N*,*N*-didodecylammonium chloride was afforded in 83% yield after crystallizing the crude in ethanol (**Scheme 9**).



Scheme 9. The chemical recycling process of **AmDTC-$C_{12}C_{12}$** to ammonium salt

Conclusion

The salt-free CatAnionic amphiphile was previously synthesized by the combination of a single-chain cationic and single-chain anionic amphiphile, from which the side product-salt must be removed. In this work, we have successfully produced a salt-free CatAnionic amphiphile of **AmDTC-$C_{12}C_{12}$** through a simple one-step condensation. The **AmDTC-$C_{12}C_{12}$** holds a unique structural difference since it contains double-chain cationic (dialkylammonium) and double-chain anionic (dithiocarbamate) amphiphile, as opposed to the single-chain amphiphile in the prior synthesis. Dispersion of the **AmDTC-$C_{12}C_{12}$** in water provided the salt-free CatAnionic vesicle that formed spontaneously without a need for external force. The **AmDTC-$C_{12}C_{12}$** vesicle showed high stability in water and can be applied as a nanoreactor for the Michael addition between nitroolefins and 1,3-dicarbonyl compounds. Twenty-three Michael adducts were synthesized with good to high yields (65–92%.). We hypothesized that the **AmDTC-$C_{12}C_{12}$** functions as both a vesicular nanoreactor and is involved in catalysis at the dithiocarbamate moiety. Preparative-scale and one-pot Michael addition by *in situ* generation of **AmDTC-$C_{12}C_{12}$** vesicle was examined and provided the Michael adducts in comparable yields with the standard procedure. This was a highlight of our method since there was no organic solvent required for both steps during the *in situ* formation of **AmDTC-$C_{12}C_{12}$** and the Michael addition. The **AmDTC-$C_{12}C_{12}$** vesicular nanoreactor was then applied for the synthesis of (±)-baclofen with 54% yields over three steps. Reusability of the **AmDTC-$C_{12}C_{12}$** using the precipitation technique was demonstrated and

allowed the reuse of the **AmDTC-$C_{12}C_{12}$** up to seven cycles. To prolong the storage of **AmDTC-$C_{12}C_{12}$**, chemical recycling was demonstrated by converting **AmDTC-$C_{12}C_{12}$** to *N*,*N*-didodecylammonium chloride by simple acidification. Finally, we anticipate that the development of this salt-free CatAnionic **AmDTC-$C_{12}C_{12}$** amphiphilic for the Michael addition in an aqueous system will significantly contribute to the advancement of research on nanoreactors and the promotion of green chemistry principles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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