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Cetyltrimethylammonium bromide-surfactant aqueous micelles as a green and ultra-rapid reactor for synthesis of 5-oxo-2-thioxo-2,5-dihydro-3-thiophenecarboxylate derivatives

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Cetyltrimethylammonium bromide-surfactant aqueous micelles as a green and ultra-rapid reactor for synthesis of 5-oxo-2-thioxo-2,5-dihydro-3-thiophenecarboxylate derivatives

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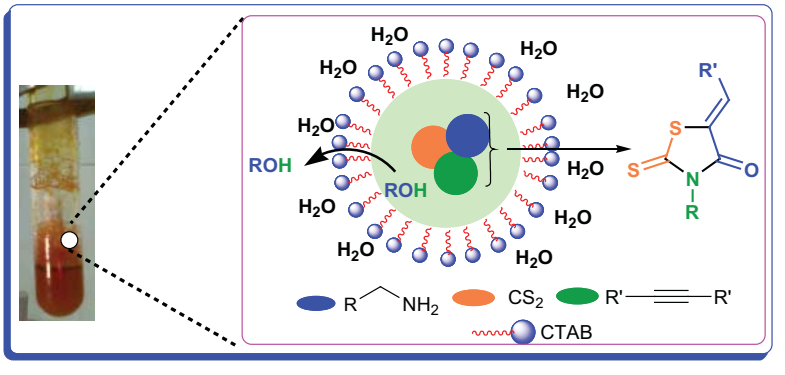
Aqueous cetyltrimethylammonium bromide-surfactant micelles were found to be an efficient and rapid reactor system for the synthesis of rhodanine by a three-component reaction of amine, carbon disulfide, and activated acetylene. The advantages of this method are the use of a water medium and a simple and easy workup resulting in a green and direct synthetic method to give excellent yields of rhodanine derivatives.



Keywords: multicomponent reaction; rhodanine; CTAB surfactant; green chemistry

1. Introduction

In recent years, based on a desire for green chemistry and an echo-friendly organic process, the use of micellar surfactants such as sodium dodecylsulfate (SDS), cetyltrimethylammonium bromide (CTAB), cetyltrimethylammonium chloride (CTAC), and cetylpyridinium chloride as the organic

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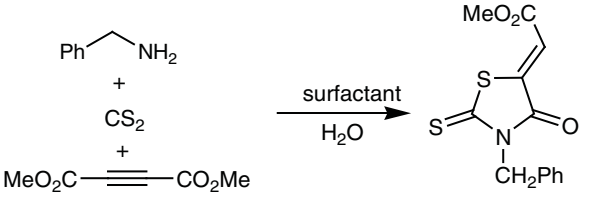
catalyst in various organic processes has attracted considerable interest (*1–4*). In particular, there has been considerable growing interest in the use of cationic, anionic, or neutral surfactants in water as normal micellar catalysts in organic synthesis (*1–5*). From the green chemistry point of view, water is the perfect solvent to carry out chemical operations since it is safe, non-toxic, and inexpensive and poses no threat to the environment (*6–10*).

One of the main objectives of organic and medicinal chemistry is the design, synthesis, and production of molecules having value as human therapeutic agents (*11*). Rhodanine-based molecules, in particular, are known to possess multiple biological activities including the inhibition of numerous targets such as Hepatitis C Virus NS3 protease (*11*) and β-lactamase (*12*). As part of our ongoing research in multicomponent reactions leading to the synthesis of heterocyclic compounds (*13–16*), and based on our previous study of the synthesis of rhodanine (5-oxo-2-thioxo-2,5-dihydro-3-thiophenecarboxylate) (*16*), we became interested in the development of a practical method to synthesize potential pharmacologically and biologically interesting rhodanines by a green aqueous micellar method (*17–21*).

2. Results and discussion

In continuation of our ongoing program aiming at the development of efficient methods for the synthesis of heterocycles with medicinal applications (*13–16*), we carried out a simple one-pot reaction for the synthesis of rhodanine under CTAB-mediated conditions in water (Scheme 1).



Scheme 1. Synthesis of rhodanines under surfactant-mediated method.

In order to evaluate the surfactant efficiency, synthesis of **3a** [the reaction of dimethyl acetylenedicarboxylates (DMAD), CS_2, and benzyl amine] as a model reaction was carried out in water medium with a catalytic amount of CTAB. To our surprise, in comparison to reaction in water that only gave a 15% yield in 10 min, the CTAB-mediated synthesis of rhodanine occurred in 95% yield within 15 min (Table 1).

Based on rapid preparation of **3** by catalytical amount of cationic surfactant (CTAB), we also used tetrabutylammonium bromide (TBAB) in the same ionic strength condition as a comparison study. As a result from Figure 1, the reaction of benzyl amine with carbon disulfide in the presence of the activated acetylene DMAD afforded rhodanines in CTAB solution condition was carried out mainly by micellar property of the CTAB.

Given the biological interest in rhodanines and after selection of the ideal reaction conditions (CTAB, 15 mol% in room temperature), we extended this reaction to the synthesis of other derivatives of rhodanine, thereby demonstrating the diversity of our method. The results are summarized in Table 2. These results support the proposed catalytic function of the surfactant.

CTAB-surfactant aqueous micelles as a green reactor for the synthesis of rhodanine derivatives have successfully been used by different derivatives of amine and acetylene. When we studied the lipophilicity of the acetylenes or amine by changing the ester or aromatic regions, we did not see strong differences in the catalytic ability of the surfactant after 15 min. As indicated in Figure 2,

Table 1. Effect of reaction conditions on model synthesis of **3a**.[a]

Surfactant	Temperature (°C)	mol%	Time (min)	Yield %[b]
SDS	rt	5	10	27
SDS	rt	10	10	36
SDS	rt	15	10	47
SDS	40	15	15	66
CTAB	rt	5	10	33
CTAB	rt	10	10	38
CTAB	rt	15	10	76
CTAB	rt	15	15	95
CTAB	rt	20	15	94
CTAB	rt	25	15	95
CTAC	rt	5	10	30
CTAC	rt	10	10	37
CTAC	rt	15	10	71
–	rt	–	10	15

Notes: [a]Reaction conditions: amine (2.4 mmol), CS_2 (3 mmol), DMAD (2 mmol), in water (8 ml).
[b]Isolated yield based on DMAD.

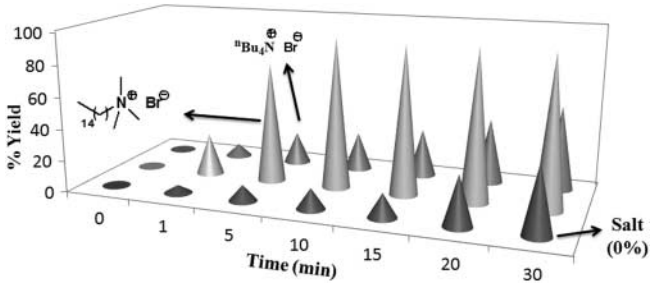
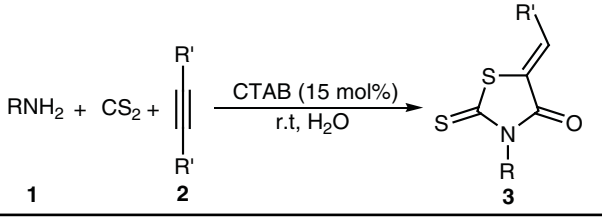


Figure 1. Reaction conditions: amine (1.2 mmol), CS_2 (1.5 mmol), DMAD (1 mmol), in water (4 ml) with CTAB (15 mol%) or TBAB (15 mol%).

Table 2. Synthesis of 5-oxo-2-thioxo-2,5-dihydro-3-thiophenecarboxylate using CTAB.[a]



1 **2** **3**

3	R	R′	Time (min)	Yield (%)[b]
a	$C_6H_5CH_2$	CO_2Me	15	95
b	*p*-Cl-$C_6H_4CH_2$	CO_2Me	15	93
c	*o*-Cl-$C_6H_4CH_2$	CO_2Me	20	92
d	*o*-Cl-$C_6H_4CH_2$	CO_2Et	20	94
e	$C_6H_5CH(CH_3)$	CO_2Me	20	92
f	$CH_3CH(CH_3)CH_2$	CO_2Me	15	91
g	$CH_2{=}CHCH_2$	CO_2Me	20	90
h	$CH_3CH(CH_3)$	CO_2Me	20	91

Notes: [a]Reaction conditions: amine (1.2 mmol), CS_2 (1.5 mmol), DMAD (1 mmol), in water (4 ml).
[b]Isolated yield based on DMAD.

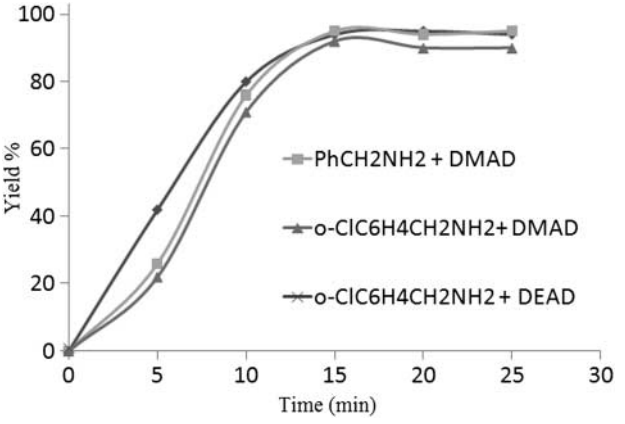
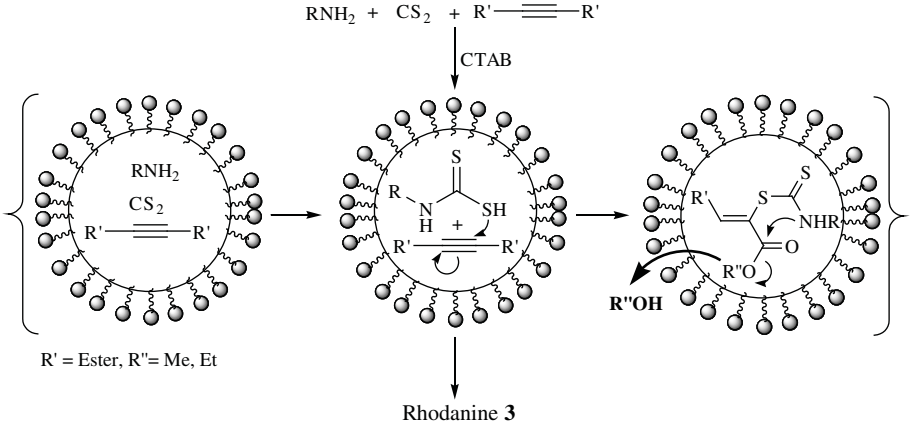


Figure 2. Reaction conditions: amine (1.2 mmol), CS_2 (1.5 mmol), DMAD or DEAD (1 mmol), in water (4 ml) with CTAB (15 mol%).

during the reaction time (spatially less than 10 min), speed of rhodanine generation depends on the nature of ester and aromatic moiety of acetylene and amines, respectively.

A proposed mechanism for CTAB-mediated synthesis of rhodanines is shown in Scheme 2. We suggest that the reaction occurs by initial formation of the dithiocarbamate by a micellar-catalyzed reaction between the amine and CS_2 (*16–18*). The dithiocarbamate then adds to the acetylene by *S*-addition of the dithiocarbamate to acetylene followed by nucleophilic attack of the dithiocarbamate nitrogen at the ester carbonyl and elimination of alcohol to form the rhodanine ring (Scheme 2).



Scheme 2. Proposed mechanism for CTAB-mediated synthesis of rhodanines.

3. Conclusion

We have described a green, simple surfactant-mediated route for the synthesis of rhodanine derivatives of potential, pharmacologically and biologically, interest. Another advantage of the present echo-friendly green procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials and that after 15–20 min, the products can be separated by simple extraction.

4. Experimental

4.1. *Chemicals and apparatus*

All reagents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Melting points were measured on an Electrothermal 9100 apparatus.

4.2. *General procedure for synthesis of rhodanine derivatives*

The amine derivative (1.2 mmol) and carbon disulfide (1.5 mmol) were added to a solution of CTAB (15 mol%) in H_2O (4 ml) and the mixture stirred at room temperature for 1 min, and then 1 mmol of activated acetylene was added to the mixture during 1 min. After completion (Table 2, TLC), the reaction mixture was extracted with CH_2Cl_2 (4×10 ml) and dried over anhydrous $MgSO_4$, and evaporated to give the rhodanine. All the products were previously reported (16, 22) and were characterized by direct comparison of their IR and physical data.

4.2.1. *Ethyl 2-[3-((4-chlorophenyl)methyl)-4-oxo-2-thioxo-1,3-thiazolan-5-yliden] ethanoate (**3b**)*

Orange powder, m.p. 115–117°C. IR (KBr) (υ_{max}, cm^{-1}): 1728 (C=O), 1649 (C=C), 1310 and 1177 (C=S). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta_H = 3.87$ (3H, s, OMe), 5.24 (2H, s, CH_2Ph), 6.84 (1H, s, C=CH), 7.28 (2H, d, $^3J_{HH} = 8.4$ Hz, 2CH of Ar), 7.37 (2H, d, $^3J_{HH} = 8.4$ Hz, 2CH of Ar) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta_C = 46.62$ (OMe), 52.89 (CH_2Ph), 117.16 (C=CH), 128. 86 (2CH of Ar), 130.49 (2CH of Ar), 132.79 (C*ipso* of Cl), 134.36 (C*ipso* of NCH2), 141.82 (C=CH), 165.45 (CON), 166.46 (CO_2Me), 195.43 (C=S) ppm.

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