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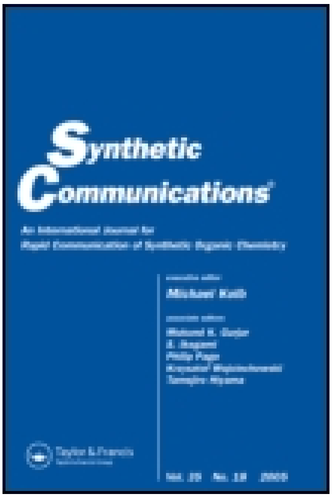

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Surfactant-Catalyzed Addition of Higher Thiols to N-Aryl Substituted Maleimides

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SURFACTANT-CATALYZED ADDITION OF HIGHER THIOLS TO N-ARYL SUBSTITUTED MALEIMIDES

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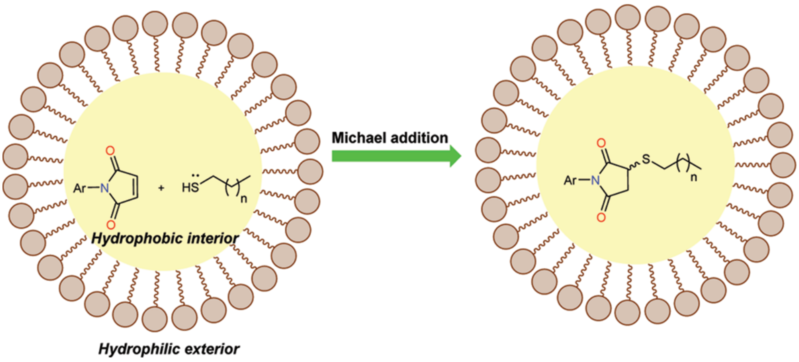
GRAPHICAL ABSTRACT



Abstract *The cationic-type surfactant-catalyzed conjugate addition reaction of long-alkyl-chained thiols with N-aryl-substituted maleimides in water as a green reaction medium afforded the corresponding thia-Michael adducts in moderate to good yields.*

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Keywords Alkyl thiols; green chemistry; *thia*-Michael addition; water

INTRODUCTION

The Michael reaction is one of the most important ways to form C-C bonds. In this reaction conjugate addition occurs between electron-poor olefins and C nucleophiles. The reaction of S nucleophiles (thiols) with polarized double bonds may be represented as a *thia*-Michael type addition for the construction of the C-S bond.[1] Numerous methods have been reported for the conjugated addition of thiols to polarized double bonds through the activation of thiol nucleophiles by bases,[1] acids,[2,3] or ionic liquid systems.[4–7] Most Michael adducts were obtained in toxic organic

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solvents.[8–10] Generally water alone is a poor solvent for the hydrophobic reagents. Surface active agents are capable adequately dissolving these reagents in water by micellar effects.

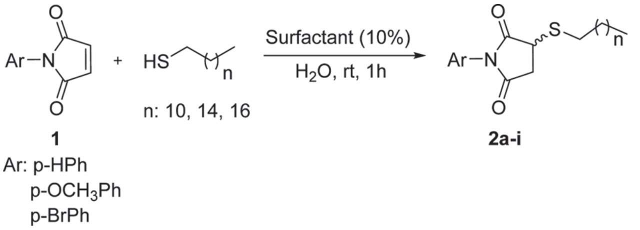
The solvent is the main component in many organic syntheses. It is used as the reaction medium, as well as for the separation and purification of the reaction product. There are many common organic solvents that have adverse health effects. Most of the halogenated solvents and benzene are strongly carcinogenic. Therefore, knowledge of alternative, greener solvents is important. Water has been successfully employed as a versatile and alternative green solvent in a variety of organic reactions and synthesis methodologies. Kumar et al. developed an efficient methodology for the addition of thiols to N-aryl maleimides.[11] They have used only water-soluble 2-mercaptoethanol and mono-halogenated aromatic thiols as nucleophiles. There are no prior studies in the literature related to Michael addition of long-hydrocarbon-chained alkyl thiols to N-aryl maleimides in water. For instance, Jegelka and Plietker used only 1-hexadecanethiol as a nucleophile in benzene solvent.

This article describes a simple and efficient one-pot procedure for the addition of higher aliphatic thiols to N-aryl-substituted maleimides using cetylpyridinium bromide (CPB) or cetyl trimethylammonium bromide (CTAB) catalyst and water as a green solvent under mild and neutral conditions. The reaction in this study proceeded efficiently at room temperature under micellar catalysis and adduct thus obtained was isolated by simple vacuum filtration.

RESULTS AND DISCUSSION

The *N*-Aryl maleimides **1** used in this study were prepared by condensation of maleic anhydride with different anilines in ether, followed by refluxing the obtained maleamic acid in acetic anhydride and in the presence of fused sodium acetate to give the corresponding maleimide. The selected alkyl thiols are insoluble in water. To facilitate their dispersion and to accelerate the reaction in water medium, CPB or CTAB were used as catalyst (10% mmol/mmol). Cationic surfactant, particularly quaternary ammonium bromide, in aqueous media has been proved to enhance the reactivity of water-mediated organic reactions via the formation of micelles or vesicular cavities.[12] As seen in Scheme 1, the addition reactions of the corresponding thiols in the presence of either CPB or CTAB proceeded with complete chemoselectivity and afforded only the desired *thia*-Michael adducts in good yields.

The experimental results are summarized in Table 1. The surfactant CPB is more soluble in water. Consequently in the presence of its catalytic activity the adducts



Scheme 1. Reaction conditions of *thia*-Michael addition.

Table 1. Aqueous *thia*-Michael addition in the presence of 10% mmol/mmol CTAB or CPB

Entry	R	Thiol (n)	Adduct	Yield[a]	Yield[b]
1	H	10	**2a**	85	98
2	p-OCH_3	10	**2b**	84	89
3	p-Br	10	**2c**	78	97
4	H	14	**2d**	80	95
5	p-OCH_3	14	**2e**	85	98
6	p-Br	14	**2f**	86	86
7	H	16	**2g**	79	82
8	p-OCH_3	16	**2h**	92	82
9	p-Br	16	**2i**	84	91

[a] Yield in the presence of CTAB after crystallization.
[b] Yield in the presence of CPB after crystallization.

were obtained with slightly great yields than in the presence of catalytic activity of CTAB. Known surfactants, like those used in this study, form a normal-phase micelle in water, and the hydrophobic interior part of this micelle acts as a reaction realization center. It provides an excellent reaction medium for Michael addition reaction by dissolving the water-insoluble *N*-aryl maleimides and higher thiols (Fig. 1). No reaction occurs in the absence of CTAB and CPB. Because the long-chain thiols are practically insoluble in water without the assistance of the surface active agents, it seems difficult

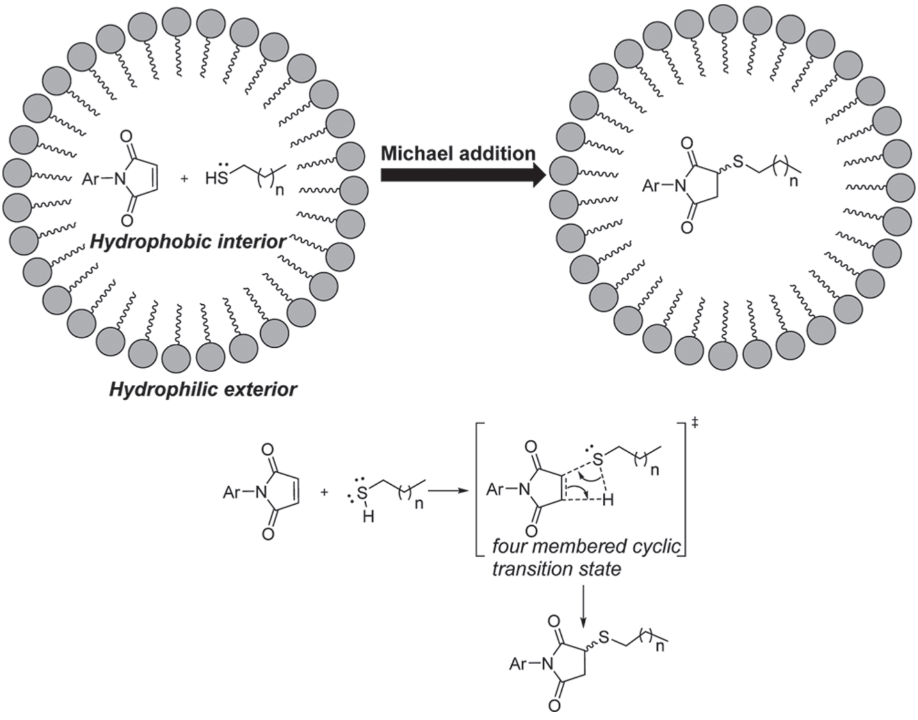


Figure 1. Possible addition mechanism via synchronous four-membered cyclic transition state.

for the reaction to proceed through an ionic mechanism. Nonionic reaction in this hydrophobic interior probably proceeds via a synchronous four-membered cyclic transition state (Fig. 1).[12–13]

As a result we can conclude that the *thia*-Michael addition reaction proceeded efficiently under milder and greener reaction conditions.

EXPERIMENTAL

Instrumentation and Materials

All reagents and solvents were purchased from either Merck or Sigma-Aldrich and used without further purification. Thin-layer chromatography (TLC) was performed using silica gel (60 F_{254}, Merck, Darmstadt, Germany) plates. Melting points were recorded on a Büchi melting point B-540 apparatus (Büchi Labortechnik AG in Flawil, Switzerland). The NMR spectra were measured using a Varian Mercury Plus spectrometer (400 MHz) (Varian Inc., California, USA) in $CDCl_3$ using telramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) and *J* values in hertz.

Typical Experimental Procedure for the Preparation of *Thia*-Michael Adducts

To a 100-mL round-bottom flask containing (40 mL) of distilled water, were added CTAB or CPB (10 mmol%) and stirred at room temperature. To this mixture 1-dodecanethiol (0.35 g, 1.56 mmol) was added in one portion, followed by N-phenylmaleimide **(1)** (0.3 g, 1.56 mmol) added portionwise. Stirring was continued for an additional 1 h at room temperature. As the reaction completed (monitored by thin-layer chromatography, TLC) the precipitated product was collected by vacuum filtration and dried at room temperature. Thereafter it was crystallized from ethanol/ethyl acetate as a white crystalline solid.

SUPPORTING INFORMATION

Structural characterization data and NMR spectra are available online.

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