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Organocatalysis in aqueous micellar medium: a new protocol for the synthesis of [1,2,4]-triazolyl-thiazolidinones

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ABSTRACT

A new environmentally friendly methodology for the efficient synthesis of biologically significant triazole thiazolidinone hybrids in aqueous medium, using acetic acid as an organocatalyst in the presence of cetyltrimethylammonium bromide (CTAB) surfactant has been developed for the first time. The effect of several surfactants on the yield and completion time of the reaction was investigated and it was found that the use of CTAB at 60 °C gave the best results (79–96% in 20 min–35 min) for the synthesis of the target compounds.

The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their use as scaffolds in the design of biologically active new compounds.[1] Thiazolidinone is one such heterocyclic moiety which is finding increasing applications in the design of new bioactive compounds,[2] chiefly antimicrobial agents.[3] 1,2,4-Triazole is another biologically important compound which is present as a key structural motif in diverse types of drug molecules and bioactive molecules.[4]

Hybrid molecules have recently come under focus due to their promising physical, chemical, and biological properties.[5] Hybrid molecules are chemical units composed of two (or more) structural domains in which the characteristics of various constituents have been altered to give rise to altogether new properties.[6]

The concept of hybrid molecules or molecular hybridization is now being increasingly used by pharmaceutical chemists in their quest for potent new drugs as evidenced by the large number of recent literature reports on the synthesis of new bioactive hybrid molecules with the goal of creating new chemical entities more medically effective than their precursors.[6,7]

Using the concept of molecular hybridization, 1,2,4-triazoles and thiazolidinones have been integrated unto one platform to obtain a new type of hybrid molecule, triazolyl-thiazolidinone, which is assumed to possess important medicinal properties. Their importance is attested by the fact that a number of workers have attempted their synthesis and the resulting hybrid-triazolyl thiazolidinones have exhibited interesting biological properties, especially anti-bacterial, anti-tubercular, anti-fungal, insecticidal etc.[8]

In the last two decades there has been a growing emphasis on the development of environmentally friendly green techniques in organic syntheses so as to reduce harm to the environment with singular emphasis on the use of water as a solvent and organocatalysts for catalyzing the reaction.[9] But the hydrophobicity of most organic substrates is a serious drawback for effecting their reactions in an aqueous environment. In this scenario the use of surfactants provides an effective way to overcome this pitfall via the formation of micelles or vesicular cavities enhancing the reactivity of water mediated reactions.[10] In micellar catalysis, the surfactant micelles act to concentrate all reacting molecules within the solution, both by solubilization due to hydrophobic effect and by counter ion binding due to electrostatic forces enhancing the efficiency as well as the rate of a chemical reaction.[11]

In the background of the above discussions we decided to devise a new, environmentally benign synthesis to access triazolyl thiazolidinones **6a–g** and **7a–g** using water as solvent, acetic acid as an organocatalyst along with a surfactant, invoking the concept of micellar catalysis to overcome the hydrophobic effect.

The synthetic strategy adopted to obtain the target compounds is presented in Scheme 1. 1,2,4-Triazole **1** reacts with benzaldehyde **2a–g** in aqueous micellar medium to afford schiff bases

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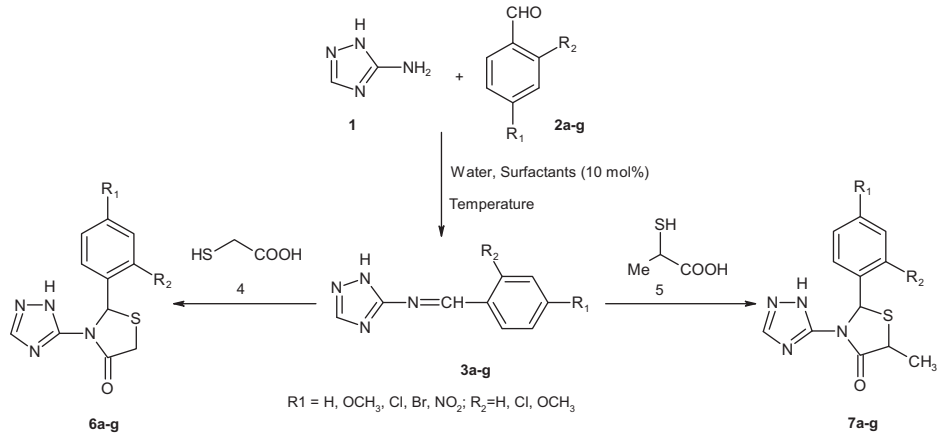
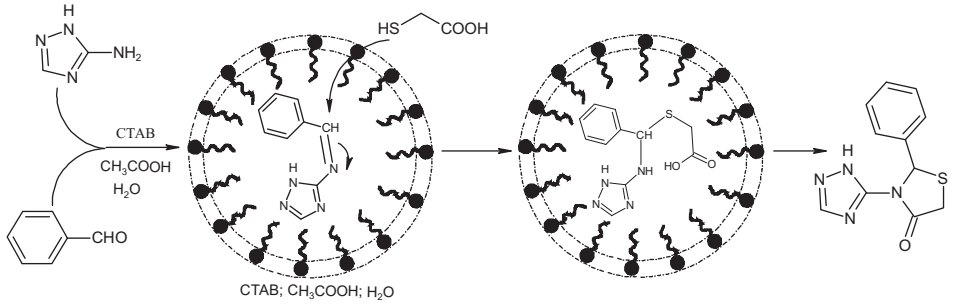


Scheme 1. Diagramatic representation of formation of triazolyl-thiazolidinones.



Scheme 2. Diagramatic representation of progress of reaction.

Table 1
Screening of surfactants[a]

Entry	Surfactant	Temp. (°C)	Time	Yield[b] (%)
1	SDS	rt	4.5 h	49
2	CPC	rt	4.0 h	22
3	MTPPB	rt	4.0 h	20
4	CTAB	rt	30 min	76
5	CTAB	60	20 min	91
6	CTAB	60	30 min	91

[a] Reaction conditions: benzaldehyde (1 mmol), [1,2,4]triazole (1 mmol), mercapto acetic acid/methyl mercapto acetic acid (1 mmol) and few drops of acetic acid, surfactant (10 mol %) in 5 ml water.
[b] Isolated yields.

3a–g which react in situ with mercapto acetic acid (**4**) or methyl mercapto acetic acid (**5**) in the presence of a few drops of acetic acid to give the corresponding substituted thiazolidinones **6a–g** and **7a–g**. The reaction proceeds by attack of sulfur nucleophile, followed by intramolecular cyclization or elimination of water (Scheme 2).

In our initial investigation a variety of surfactants were screened in order to identify the best surfactant for catalyzing this reaction (Table 1). Consequently, different cationic surfactants such as cetyltrimethylammonium bromide (CTAB), cetylpyridinium chloride (CPC), and methyltriphenylphosphonium bromide (MTPPB) as well as an anionic surfactant, sodium dodecyl sulfate (SDS), were employed. It was observed that the cationic surfactants, CPC and MTPPB and the anionic surfactant, SDS gave the desired product in low yields 22%, 20%, and 49%, respectively. In contrast, the cationic surfactant, CTAB accelerated the model reaction to afford the desired product in excellent yield −76% in 30 min at rt and 91% in 20 min at 60 °C (Table 1, entries 4 and 5). These results revealed that cationic surfactants performed better presumably due to stronger binding of the CTAB to the substrate.

The structures of the synthesized compounds were confirmed by spectral data and elemental analysis and were in full agreement with the proposed structure. The ^{1}H NMR spectra of compound **6a** showed the presence of doublet signals at δ 3.32, 3.40 ppm for the two protons of –S–C*H*$_2$– and a singlet at δ 5.99 ppm for –S–C*H*–N– which confirms the formation of the thiazolidinone ring.

Once the reaction conditions have been optimized for obtaining the target triazolyl-thiazolidinone hybrids in good yield and short reaction time, the developed synthetic protocol was used to access a series of triazolyl-thiazolidinones, **6a–g**, **7a–g**, which were obtained in excellent yields ranging from 79% to 96% (Table 2).

In summary, we have reported a new environmentally friendly methodology for the synthesis of triazole thiazolidinone hybrids: substituted-2-phenyl-3-(1*H*-1,2,4-triazol-5-yl)thiazolidin-4-one (**6a–g**) and 5-methyl-substituted-2-phenyl-3-(1*H*-1,2,4-triazol-5-yl)thiazolidin-4-one (**7a–g**) in aqueous medium employing acetic