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Facile and regioselective synthesis of thiazolidin-4-one derivatives catalyzed by basic ionic liquid [bmim]OH under ultrasonic irradiation

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SHORT COMMUNICATION

Facile and regioselective synthesis of thiazolidin-4-one derivatives catalyzed by basic ionic liquid [bmim]OH under ultrasonic irradiation

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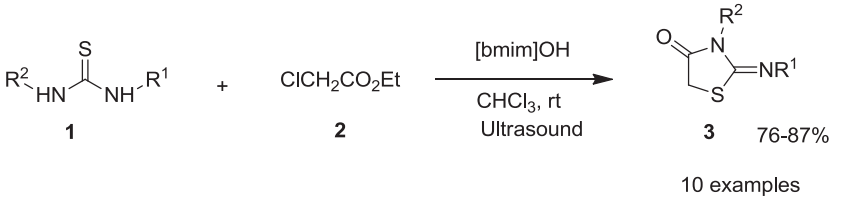
2-Iminothiazolidin-4-one derivatives were synthesized regioselectively in good to high yields by condensation of *N*,*N*-disubstituted thioureas and ethyl chloroacetate in the presence of basic ionic liquid [bmim]OH as a catalyst under conventional and ultrasonic irradiation conditions. Under ultrasonic irradiation, the reaction furnished the desired 2-iminothiazolidinones in higher yields (76–87%) and lower reaction times (30–55 min).



R^1 = 4-CH_3-C_6H_4, C_6H_5-CH_2, CH_2=$CHCH_2$, 4-EtO-C_6H_4, 4-Et-C_6H_4, 4-F-C_6H_4

R^2 = CH_2=$CHCH_2$, C_6H_5-CH_2

Keywords: regioselective; ionic liquid [bmim]OH; thiazolidin-4-one; ultrasound, thiourea

1. Introduction

Thiazolidinones (TZDs) and their derivatives are an important group of heterocyclic compounds, having valuable biological activities in the areas of medicine and agriculture (*1*). They have found uses, for example, as insecticides, tuberculostatic (*2*), anti-inflammatory (*3*) and antiviral agents (*4*). In recent years, 4-thiazolidinones are among the most extensively investigated heterocycles. TZDs have been the subject of extensive researches because of their deep involvement in the regulation of different physiological processes. Thiazolidinedione derivatives have been shown to possess potent immunostimulatory property, anti-arthritic activity as well as oncostatic activity (*5*). TZDs such as troglitazone, pioglitazone and rosiglitazone are potent reducers of

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plasma glucose level *in vivo*. Besides their anti-diabetic potency, these compounds have been shown to exert anti-inflammatory effects on vascular cells (*6*). TZDs were also found to inhibit the production of inflammatory cytokines and the expression of inducible nitric oxide syntheses in monocytes/macrophages (*7*, *8*). In addition, the potent activity of 2-imino-4-thiazolidinones has established them as important structure elements in medicinal chemistry (*9–13*). These products have demonstrated significant antiviral, pesticidal, bactericidal, insecticidal, antiproliferative, antihistaminic, fungicidal, tuberculostatic, anticonvulsant, anticancer, anti-inflammatory, Ca^{2+} antagonist, SHP-2 inhibitor and PTC readthrough activities (*14–20*).

Several synthetic methods have been reported for the synthesis of 2-imino-4-thiazolidinones (*21–25*). However, some of these methods use expensive starting materials, harsh reaction conditions, long reaction times and low yields. Therefore, the development of an efficient and versatile method is still required.

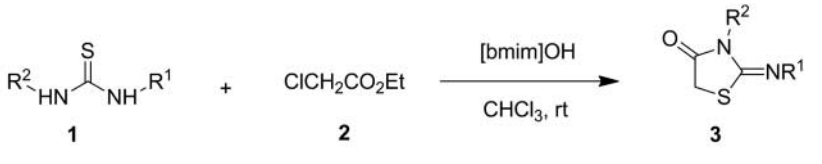
On the other hand, ionic liquids have attracted extensive interest as environmentally friendly catalysts as well as excellent alternatives to organic solvents, due to their favorable properties. The use of ionic liquids as the reaction medium may offer a convenient solution to both the solvent emission and the catalytic recycling problem and results in minimal pollution and waste material production (*26–30*).

These observations led us to attempt the synthesis of some new 2-iminothiazolidin-4-one derivatives using of *N*,*N*-disubstituted thioureas and ethyl chloroacetate in the presence of basic ionic liquid [bmim]OH as a catalyst under conventional and ultrasonic irradiation conditions.

2. Results and discussion

As part of our program aimed at developing highly expedient, selective and environmentally friendly methodologies for the preparation of heterocyclic compounds (*31*), we describe here an efficient method for the regioselective synthesis of new derivatives of thiazolidin-4-one under conventional conditions and ultrasounic irradiations in the presence of basic ionic liquid [bmim]OH as a catalyst.

The requisite disubstituted thioureas (**1**) were prepared by the addition of amines to *N*-substituted isothiocyanates in $CHCl_3$ at room temperature. Stirring a mixture of equimolar amounts of **1** and ethyl chloroacetate in $CHCl_3$ in the presence of ionic liquid [bmim]OH (0.15 g/1 mmol substrate) at room temperature afforded derivatives of thiazolidin-4-one **3a**–**j** in a regioslective cyclization reaction (Scheme 1).



R^1 = $CH_3C_6H_4$, $C_6H_5CH_2$, CH_2=$CHCH_2$, C_2H_5O-C_6H_4, $C_2H_5C_6H_4$, FC_6H_4

R^2 = CH_2=$CHCH_2$, $C_6H_5CH_2$

Scheme 1. Schematic diagram showing the synthesis of thiazolidin-4-one **3a**–**j**.

To optimize the reaction conditions, preparation of **3a** as a model reaction was attempted in several solvents (1,4-dioxane, H_2O, EtOH, THF) and catalysts (Et_3N, DBU, pipyridine, L-prolin, $NaHCO_3$, AcOH) (Tables 1 and 2). The best results (73% yield) were obtained when ionic liquid

Table 1. Effect of various catalysts in the synthesis of **3a**.

Entry	Catalyst	Yield (%)[a]
1	DBU	60
2	Ionic liquid [bmim]OH	73
3	L-Proline	45
4	$NaHCO_3$	40
5	Et_3N	40
6	Piperidine	15

Note: [a]Isolated yield.

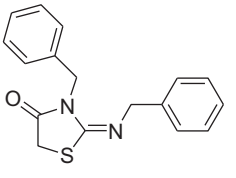
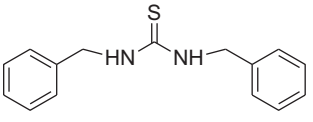
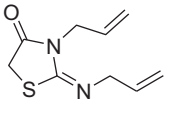
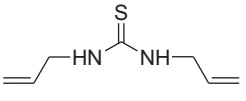
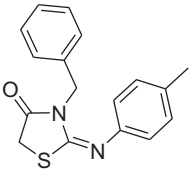
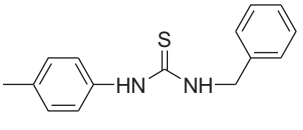
Table 2. Effect of various solvents in the synthesis of **3a**.

Entry	Solvent	Yield (%)[a]
1	H_2O	0
2	$CHCl_3$	73
3	1,4-dioxane	45
4	THF	55
5	EtOH	20

Note: [a]Isolated yield.

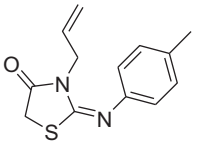
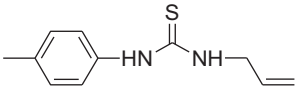
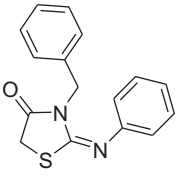
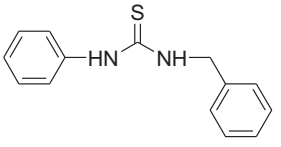
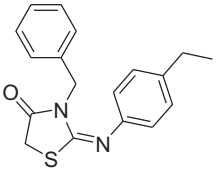
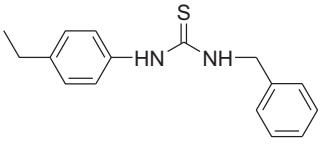
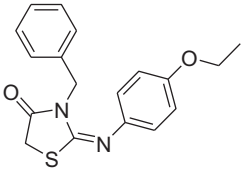
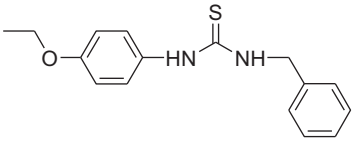
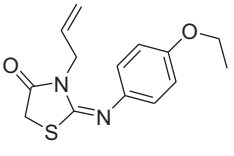
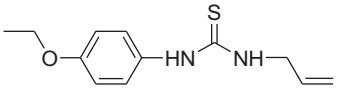
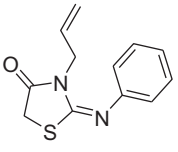
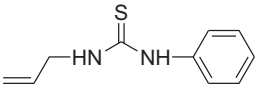
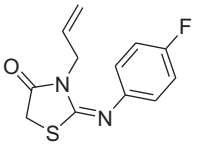
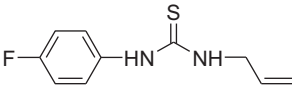
[bmim]OH was used as a catalyst in $CHCl_3$ after 24 h stirring at room temperature (Tables 2 and 3). We also verified the amount of catalyst in the preparation of **3a** in $CHCl_3$ and the best result was obtained using 0.15 g ionic liquid [bmim]OH for 1 mmol substrate.

Table 3. Synthesis of products (**3a–j**).

			Conventional[a]	Ultrasound	
Entry	Product	Thiourea	Yield(%)[a,b]	Yield (%)[b]	Time (min)
3a			73	78	50
3b			79	81	55
3c			80	87	30

(*Continued*)

Table 3. Continued

Entry	Product	Thiourea	Conventional[a] Yield(%)[a,b]	Ultrasound Yield (%)[b]	Ultrasound Time (min)
3d			76	80	40
3e			75	80	45
3f			78	82	45
3g			74	78	40
3h			72	76	45
3i			80	86	40
3j			83	85	35

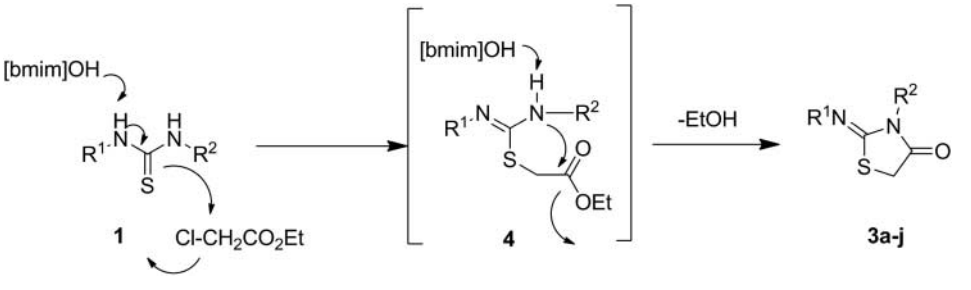
Notes: [a]Reaction time 24 h at room temperature.
[b]Isolated yield.

Recently, there has been an increasing interest in using ultrasonic irradiations as a clean, green and environmentally benign source of energy for the preparation of organic compounds of synthetic and biological value (*32*). Encouraged further by our recent findings in facilitating the

synthesis of important heterocyclic compounds by exploiting ultrasound methodology (*31a, b*), we investigated the effect of ultrasonic irradiation on the synthesis of novel thiazolidin-4-one **3a**–**j**. Therefore, an equimolar mixture of reactants **1** and **2** in the presence of basic ionic liquid [bmim]OH (*33*, *34*) (0.15 g/mmol substrate) in $CHCl_3$ (5 ml) was placed in a Pyrex-glass open vessel and irradiated at room temperature by ultrasonic irradiations (40 kHz) to furnish the desired products (**3a**–**j**) in lower reaction times (30–55 min) and in good to high yields (76–87%) (Table 3).

For unsymmetrical thioureas, regiocontrol in cyclization step is typically influenced by electronic factors that predispose electron-withdrawing substituents to maintain conjugative stabilization with imine nitrogen (R^1 in structure **3**). For example, in the case of **3c**–**j**, the NH proton flanked by a phenyl moiety is more acidic compared to the other NH proton flanked by benzyl or allyl moiety; therefore, enolization of thiourea from the phenyl side of the substrate is facilitated. This allows regioselective cyclization of thiourea bearing one alkyl and one aryl substituent (*21*).

A plausible mechanism for the formation of **3a**–**j** is outlined in Scheme 2. The formation of these products can be visualized by addition of ionic liquid [bmim]OH as a base catalyst and producing intermediate **4** which then cyclizes and loses EtOH to furnish the desired thiazolidin-4-one **3a**–**j**.



Scheme 2. Mechanism of synthesis of products **3a**–**j**.

3. Conclusion

In conclusion, we have developed a simple and efficient protocol for the synthesis of novel derivatives of thiazolidin-4-one catalyzed by ionic liquid [bmim]OH **3a**–**j** in a regiochemical manner at room temperature under ultrasonic irradiations and conventional conditions. The reaction induced by ultrasound offered better yields and much lower reaction times than the reaction carried out by conventional heating. This method involves mild reaction conditions, easy work-up and cleaner reaction profiles.

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Supporting information available

Supporting information is available on the publisher's website at http://dx.doi.org/10.1080/17415993.2013.800061

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