



Molecular iodine in [bmim][BF₄]: a highly efficient green catalytic system for one-pot synthesis of 1,3-oxathiolan-5-one

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ABSTRACT

Aldehydes and mercaptoacetic acid are coupled in the presence of a catalytic amount of economical and non-toxic molecular iodine in [bmim][BF₄] ionic liquid under mild conditions to afford the corresponding 1,3-oxathiolan-5-one in excellent yields. Molecular iodine acts faster in ionic liquids when compared to conventional solvents such as DMSO, DMF, ethyl acetate, and acetonitrile. The recovered ionic liquids can be recycled in subsequent reactions with consistent activity.

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Ionic liquids are rapidly becoming green alternatives to the conventional and environmentally detrimental volatile organic solvents.¹ Recently, they have attracted a great deal of attention due to their high thermal stability, good conductivity, non-volatility, non-flammability, suitable polarity, wide electrochemical window, and recyclability.^{2–8} The ionic liquids based on imidazolium cations are especially favorable for green industrial applications.⁹ These classes of ionic liquids have especially low volatility at room temperature, one reason that ionic liquids are often considered than traditional organic solvents.¹⁰ Moreover, when an ionic liquid is used as a reaction media, the solute is solvated homogeneously by ions only. Thus, the reaction can proceed in an environment totally different from that when water or ordinary organic solvents are used and as a result high selectivity is possible.¹¹ Oxathiolan-5-one derivatives are of great interest because they exhibit a broad spectrum of biological activities and are important heterocycles occurring in natural and medicinal molecules. They are intermediates in the synthesis of many bioactive compounds.¹² To exemplify, derivatives of 2-(hydroxy-methyl)-1,3-oxathiolan-5-ones can be used as building blocks for the preparation of the oxathiolanyl-nucleoside Coviracil.^{13–15} Yadav and Rai have used 2-methyl-2-phenyl-1,3-oxathiolan-5-one for high yield synthesis of polyfunctionalised bicyclic pyrimidines, which are of industrial as well as biological importance.¹⁶ 2-Amino-1,3-thiazines and their derivatives with antibacterial, antitumour, insecticidal, and fungicidal activities have also been prepared using 2-methyl-2-phenyl-1,3-oxathiolan-5-one in a green synthesis approach.¹⁷ 1,3-Oxathiolan-5-ones and their derivatives have been synthesised conventionally from disconnection approach using synthetic equivalents; a derivative of a ketone and mercaptoacetic acid employing vigorous heating with PTSA.¹⁸ Yadav et al.

have used LiBr to catalyze the reaction between acetophenone and mercaptoacetic acid to produce 2-methyl-2-phenyl-1,3-oxathiolan-5-ones in substantial yields.¹⁹ 2-Trifluoromethyl-1,3-oxathiolan-5-ones, which are potential synthetic equivalents for obtaining fluorinated analogs of biologically active compounds have also been synthesized by Tolmachev and co-workers by a two-step process employing zinc chloride.²⁰ However many of these methods seem to have technical limitations, such as, long reaction times, difficult workup, and formation of over-oxidation products leading to lower yields, requirements of strong oxidizing agents, strong acidic or basic media, use of expensive, toxic, and explosive (LiBr) reagents. As the aforesaid conditions are not compatible with heat or acid sensitive substrates, there is a compelling need to develop an effective synthetic procedure for synthesizing 1,3-oxathiolan-5-one derivatives under more eco-friendly conditions. Our reaction is more environmentally benign as compared to the reactions described above. As part of our ongoing interest in exploring various green methods for organic transformations, we disclose herein our results for the synthesis of 1,3-oxathiolan-5-one derivatives using catalytic amounts of molecular iodine in ionic liquid as an inexpensive, versatile, non-toxic, and a readily available catalyst that can serve as a green alternative method for this important reaction. Iodine in ionic liquid was already reported^{21–24} but we report here, for the first time, the use of iodine in ionic liquids as a novel and recyclable polar reaction media for the synthesis of 1,3-oxathiolan-5-one derivatives using aldehydes and mercaptoacetic acid (Table 1). In a general reaction, treatment of benzaldehyde with mercaptoacetic acid in hydrophilic ionic liquid, [bmim][BF₄] afforded 1,3-oxathiolan-5-one in 95% yield (Table 1, entry 1).

The reaction was very clean and took only 3 h at room temperature. Various aldehyde derivatives with different electron donating/withdrawing groups) reacted with mercaptoacetic acid in the presence of catalytic amounts of molecular iodine (in ionic liquid) to give the corresponding 1,3-oxathiolan-5-one derivative in high

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Table 1
Synthesis of 1,3-oxathiolan-5-one derivatives^{a,b}

S. No	Aldehydes	Product	Time (h)	Yield (%)	Mp ^c (°C)
1			3	95	87
2			3	92	130
3			4	98	132
3			3.5	67	–
4			3	58	–
5			4	68	–
6			4	90	150
7			3	87	244
8		–	–	–	–

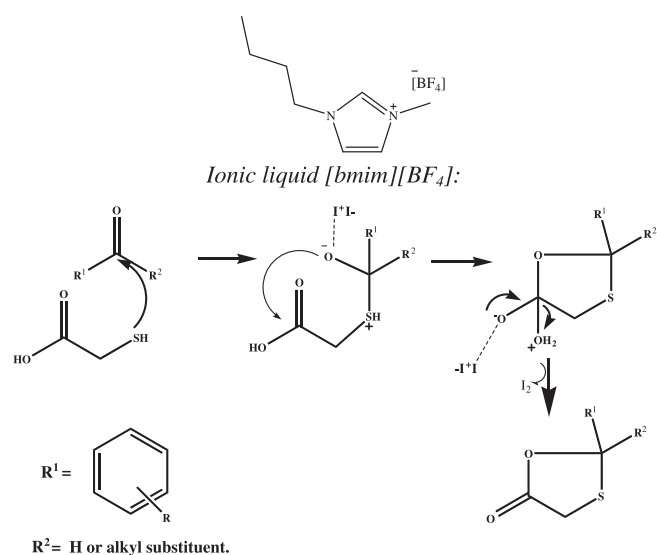
^a Reaction condition: 10 mmol of aldehyde and 10 mmol of mercaptoacetic acid catalyzed by 1 mmol of molecular iodine in 5 ml ionic liquid at room temperature.

^b Confirmed by (FT-IR, TLC, ¹H NMR and ¹³C NMR).

^c Isolated pure.

yields (Table 1).²⁵ In all cases, the reactions proceeded readily at room temperature with high efficiency. Therefore, the prime focus of this letter is on the synthesis of biologically active 1,3-oxathiolan-5-one derivatives using molecular iodine as an inexpensive and versatile catalyst, in ionic liquid as a reaction media. The results obtained are hereby incorporated in Table 1 and the proposed reaction mechanism is shown in Scheme 1.

In order to elucidate the role of molecular iodine, a controlled reaction was carried out using mercaptoacetic acid and benzaldehyde in ionic liquid without using molecular iodine. The reaction did not proceed even after 48 h and no products were formed. It is to be noted that the reaction proceeded to give ~50% yields (and took 12 h) when iodine was used alone in the absence of an ionic liquid. It is important to note that electronic factors played an important role in this iodine mediated condensation reaction in ionic liquid as a reaction media. In order to elucidate the role of the solvents, various solvents were screened to evaluate the scope and limitation of this reaction. The result substantiates our hypothesis that the iodine catalyzed synthesis of 1,3-oxathiolan-5-one derivatives would not only be faster but would also result in higher yields in ionic liquids as compared to other conventional solvents. It is interesting to note that the yield of the products is rather low in the case of polar aprotic solvents such as DMF and DMSO (Table 2). In solvent free conditions the conversion rate was found to be negligible. Clearly, ionic liquid stands out as the solvent of choice, with its fast conversion and quantitative yield.



Scheme 1. Proposed mechanism of the one-pot synthesis of 1,3-oxathiolan-5-one derivatives using molecular iodine as catalyst in ionic liquid.

The mechanism of 1,3-oxathiolan-5-one formation suggests that, iodine plays a key role in the reaction by polarizing the

Table 2
Effect of various solvents^{a,b}

Entry	Solvent	Reaction time (h)	Yield (%)
1	DMF	14	45
2	Ethylacetate	10	75
3	DMSO	15	49
4	[bmim][BF ₄]	3	95
5	Acetonitrile	9	87

^a Reaction condition: 10 mmol of benzaldehyde and 10 mmol of mercaptoacetic acid catalyzed by 1 mmol of molecular iodine in 5 ml ionic liquid at room temperature.

^b Confirmed by (FT-IR, TLC, ¹H NMR and ¹³C NMR).

Table 3
Recyclability of ionic liquid

Table 1 entry 1	Run 1	Run 2	Run 3	Run 4	Run 5
Yield (%)	95	95	94	92	90

carbonyl group of the substrate, thereby enhancing the electrophilicity of the carbonyl carbon. This facilitates the nucleophilic reaction of the sulfohydro group of the mercaptoacetic acid. It also illustrates the enhanced reactivity of the carbonyl substrate in case of electronic withdrawing groups in the first step and electron donating groups in the second step. However the results show, that the reactivity of the substrate is effectively increased in the cases when we employ electron donating groups, for example, in the attack of mercaptoacetic acid on anisaldehyde (Table 1, entry 3) and is drastically reduced in cases when electron withdrawing groups are present, for example, in *ortho*-, *meta*-, and *para*-nitro-substituted benzaldehydes (Table 1, entry 4–6). The results indicate that the first step, that is, the attack of nucleophilic thiol group on electrophilic carbon of the carbonyl compound is the rate determining step in the synthesis of 1,3-oxathiolan-5-one.

The advantage of using ionic liquid is that the products of the reaction can be extracted into the organic solvent, ethyl acetate leaving the ionic liquid behind which can be successfully recycled. These are quite contrary to dipolar aprotic solvents which are difficult to remove from the product.

We have developed a relatively quicker and greener method for synthesizing 1,3-oxathiolan-5-one under solvent free conditions using molecular iodine as a catalyst. The efficacy of the reaction lies in its high yield, ambient conditions of temperature, and recyclability of the reaction media, that is, the ionic liquid (Table 3).

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- General procedure for synthesis of 1,3-oxathiolan-5-ones derivatives.* A mixture of aromatic aldehyde (10 mmol), mercaptoacetic acid (0.7 ml, 10 mmol) and catalytic amount of iodine (1 mmol) in ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate (5 ml) was stirred for 3 h at room temperature. The mixture was then extracted thrice with 10 ml of ethyl acetate and the combined organic extracts were treated with an aqueous solution of Na₂S₂O₃ (1 M) and washed with saturated solution of NaHCO₃. Drying of the organic layer in vacuum afforded a crude product, which was then recrystallised with water to yield pure crystalline 1,3-oxathiolan-5-ones. The ionic liquid residue was washed with hexane and dried in vacuum resulting in recycled ionic liquid, [bmim][BF₄] (Table 3).
Characterization data of some important compounds. 2-Phenyl-1,3-oxathiolan-5-one (Table 1, entry 1). IR (KBr) ν_{\max} : 2974, 2930, 1726, 1474, 1027 cm⁻¹. ¹H NMR (DMSO-*d*₆/TMS) δ : 3.43 (d, 1H, *J* = 16.4 Hz, CH₂), 3.43 (d, 1H, *J* = 16.4 Hz, CH₂), 5.4 (s, 1H, CH), 7.3–7.7 (m, 5H_{arom}). ¹³C NMR (DMSO-*d*₆/TMS) δ : 38.2, 91.2, 126.9, 128.4, 128.9, 138.3, 171.0.
2-(4-Chlorophenyl)-1,3-oxathiolan-5-one (Table 1, entry 2). IR (KBr) ν_{\max} : 2976, 1718, 1388, 1156 cm⁻¹. ¹H NMR (DMSO-*d*₆/TMS) δ : 3.40 (d, 1H, *J* = 16.4 Hz, CH₂), 3.25 (d, 1H, *J* = 16.4 Hz, CH₂), 5.31 (s, 1H, CH), 7.4–7.9 (m, 5H_{arom}). ¹³C NMR (DMSO-*d*₆/TMS) δ : 38.2, 91.2, 128.8, 130.3, 132.2, 136.4, 175.0.
2-(4-Methoxyphenyl)-1,3-oxathiolan-5-one (Table 1, entry 3). IR (KBr) ν_{\max} : 2960, 1726, 1510, 1340 cm⁻¹. ¹H NMR (DMSO-*d*₆/TMS) δ : 3.74 (s, 3H, CH₃), 3.41 (d, 1H, 16.4 Hz, CH₂), 3.28 (d, 1H, 16.4 Hz, CH₂), 6.28 (s, 1H, CH), 6.77–7.46 (m, 5H_{arom}). ¹³C NMR (DMSO-*d*₆/TMS) δ : 40.1, 56.0, 91.2, 115.4, 131.1, 133.1, 167.2, 178.0.
2-(2,5-Dimethoxyphenyl)-1,3-oxathiolan-5-one (Table 1, entry 6). IR (KBr) ν_{\max} : 2928, 2836, 1701, 1497, 1279 cm⁻¹. ¹H NMR (DMSO-*d*₆/TMS) δ : 3.76 (s, 3H, CH₃), 3.88 (s, 3H, CH₃), 3.43 (d, 1H, *J* = 16.4 Hz, CH₂), 3.26 (d, 1H, *J* = 16.4 Hz, CH₂), 5.58 (s, 1H, CH), 6.78–7.45 (m, 5H_{arom}). ¹³C NMR (DMSO-*d*₆/TMS) δ : 38.4, 56.3, 81.6, 113.5, 115.5, 124.9, 154.1, 154.8, 174.5.