



An atom-economic and odorless thia-Michael addition in a deep eutectic solvent



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ABSTRACT

The first 100% atom-efficient and odorless protocol for carbon–sulfur bond formation in a deep eutectic solvent (DES) as both the reaction medium and catalyst is reported. The biodegradable and inexpensive DES provides an efficient and convenient ionic reaction medium for the thia-Michael addition with in situ generation of *S*-alkylisothiuronium salts in place of thiols without the urea by-product segment. This protocol offers several advantages including short reaction times, high yields, clean reactions, and inexpensive and commercially available starting materials.

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Organic reactions in sustainable reaction media such as ionic liquids, without the use of harmful organic solvents, have attracted a great deal of attention. These solvents are easily available and safe, especially in relation to environmental concerns. Deep eutectic solvents (DESs) have many advantageous properties compared to common organic solvents. They have physicochemical properties of room-temperature ionic liquids (RTILs) such as negligible vapor pressure, high thermal and chemical stabilities, non-flammability, and high solvation capacity. However, DESs have many advantages over ILs such as simple preparation, low price, chemical inertness to water, high atom economy, and avoid purification problems and waste disposal encountered with common ILs. Furthermore, they can be made from biodegradable components, with 100% atom economy.¹

Green carbon–sulfur bond formation under safe and eco-friendly conditions, to give intermediates that can be converted into commercially important biological and pharmaceutical products has attracted significant attention.² Thiol-containing organic compounds such as cysteine, glutathione, and cysteamine play important roles in living organisms, and are involved in a number of biological processes due to the properties of the thiol function. They have found various applications as enzyme inhibitors and biologically active calcium antagonists, and abnormal levels of these species are closely related to certain diseases.³

Consequently, a large number of reagents and catalysts have been reported in the literature for the reactions of mercaptans with

a variety of electrophilic reagents such as conjugated alkenes, epoxides, and alkyl halides.⁴ Although some of these reported procedures are effective on small scale, the use of highly toxic, volatile, and foul-smelling thiols could lead to serious environmental and safety problems in large scale reactions. Therefore, several attempts have been made to develop odorless protocols in order to prevent environmental pollution and decrease the stress of researchers working with them.⁵

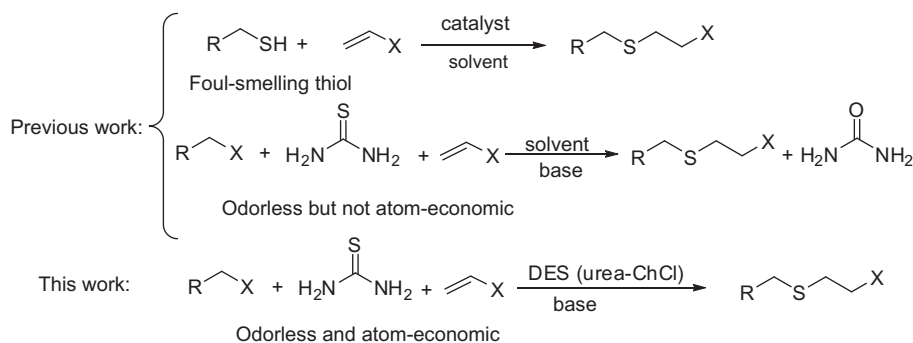
In this context, several recent publications are notable as they have reported odorless thiol equivalents such as the use of *S*-alkylisothiuronium salts, to give thiols. However, this odorless thiol equivalent has poor atom economy, which is an important concept of green chemistry. The reaction produces equivalent amounts of urea, which need to be separated from the product and disposed of as waste.⁶ As a consequence, there is scope to search for a more user-friendly and atom-economic reaction. This observation and our interest in the development of new methodologies using green solvents, prompted us to investigate carbon–sulfur bond formation through the in situ generation of *S*-alkylisothiuronium salts in place of thiols, without the formation of a urea by-product (Scheme 1).

Based on our interest in deep eutectic solvents,⁷ we describe herein an odorless, atom-economic route for the preparation of β -keto sulfides via the one-pot reaction of thiourea, alkyl halides, and electron-deficient olefins in a choline chloride based deep eutectic solvent, under safe and eco-friendly conditions.

In the initial attempt, and to optimize the reaction conditions, the one-pot reaction of benzyl chloride and thiourea with methyl acrylate was examined in a choline chloride–urea based DES under

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Scheme 1. General carbon–sulfur bond forming reactions in the literature reported in this work.

Table 1
 Optimization of the reaction conditions in model reaction

Entry	Additive (x mmol)	Time (h)	Temp (°C)	Yield ^{a,b} (%)
1	—	4	rt	0
2	NaHCO ₃ (1 mmol)	4	60	29
3	K ₂ CO ₃ (1 mmol)	4	60	56
4	Et ₃ N (1 mmol)	4	60	30
5	DBU (1 mmol)	4	rt	0
6	Na ₂ CO ₃ (1 mmol)	4	60	55
7	NaOH (1 mmol)	4	rt	0
8	NaOH (1.5 mmol)	4	rt	0
9	NaOH (2 mmol)	4	rt	0
10	NaOH (2 mmol)	1	60	30
11	NaOH (0.1 mL)	1	60	69
12	NaOH (0.2 mL)	1	60	73
13	NaOH (0.4 mL)	1	60	95
14	NaOH (0.4 mL)	1	80	95
15	NaOH (0.4 mL)	1	100	95

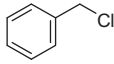
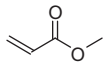
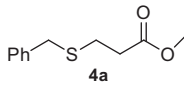
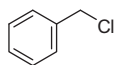

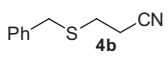
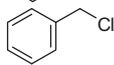
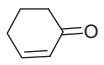
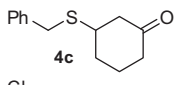
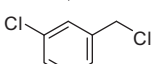

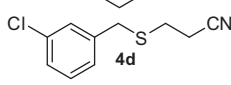
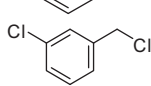
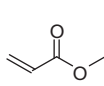
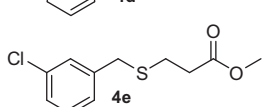
^a Isolated yields.

^b Reaction conditions; benzyl chloride (1 mmol), thiourea (1 mmol), methyl acrylate (1 mmol), DES (0.5 mL), NaOH (8 M); DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

basic conditions (K₂CO₃, Na₂CO₃, NaHCO₃, triethylamine, NaOH, DBU) (Table 1). It turned out that this three-component reaction could be carried out in the presence of NaOH and K₂CO₃ as bases in the DES at room temperature. It was also found that this reaction was significantly affected by the reaction temperature. While this process needed as long as four hours to be complete at room temperature, in the presence of 0.4 mL of 8 M NaOH, full conversion of the starting material occurred in only one hour at 60 °C (Table 1, entry 13).

Using the optimized reaction conditions, we investigated the scope of this odorless and atom-economic thia-Michael addition with various combinations of substrates, and the results are summarized in Table 2. In general, different alkyl halides **1** as well as Michael acceptors **3** could be applied successfully in this procedure, providing a diverse set of thia-Michael products under mild reaction conditions. A variety of α,β-unsaturated compounds such as, methyl acrylate, acrylonitrile, methyl vinyl ketone, and cyclohex-2-enone underwent the 1,4-addition smoothly with a wide range of alkyl halides, in short reaction times, to afford the corresponding products (**4a–4n**) in high yields. Alkyl chlorides, bromides, and iodides, as well as primary, secondary allylic and benzylic halides participated in this reaction to give the corresponding products in good to excellent yields. In addition, the reaction was tolerant of a range of functional groups including methoxy, halides, and C=C in the electron-deficient olefins and alkyl halides.

Table 2
 One-pot thia-Michael addition using alkyl halides, thiourea, and electron-deficient alkenes in a DES

Entry	Alkyl halide	Electron-deficient alkene	Product	Time (min)	Isolated yield ^a (%)
1				80	93
2				80	91
3				100	75
4				80	92
5				80	95

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