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Thia-Michael addition in a Brønsted acidic deep eutectic solvent

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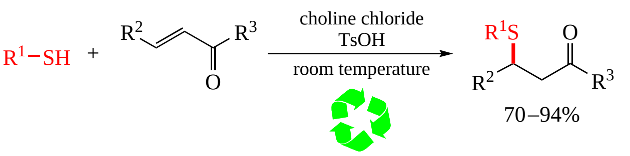
A 100% atom-efficient thia-Michael addition process between thiols and α,β-unsaturated carbonyl compounds in a Brønsted acidic deep eutectic solvent at room temperature has been developed. The medium, choline chloride/*p*-toluenesulfonic acid, not only showed good catalytic activity, but also could be readily recovered and reused with slight decrease in its activity after successive five runs.



Keywords: thia-Michael addition, C–S bond formation, sulfides, α,β-unsaturated carbonyl compounds, deep eutectic solvent, atom economy, green chemistry.

Sulfur-containing compounds are versatile intermediates due to their potential applications as novel pharmaceutical, agricultural and chemical agents.[1,2] The thia-Michael addition is one of the most convenient and useful approaches for the construction of C–S bonds. Significant achievements have been made in last decades by the use of diverse catalysts and reaction media.[3–15] Among them, the choice of thiol surrogates and reaction media is the core concern of the researchers. Although the combination of alkyl halides and thiourea[5] as well as Bunte salt[10] can be employed as the odorless thiol surrogates, the former required the use of additional bases, while the latter required pre-preparation of the starting materials.

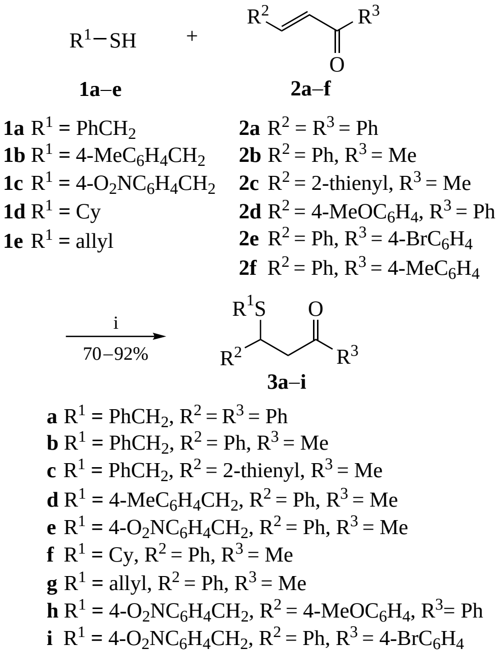
Recently, the use of green solvents such as ionic liquids[12,14] and deep eutectic solvents (DESs)[5] in thia-Michael addition has attracted much attention. Good catalytic activity as well as easy recovery of these solvents allow the reactions to be efficient and sustainable. Compared with ionic liquids, DESs possess good availability and biodegradability, low flammability and low toxicity.[16,17] They can be prepared from diverse quaternary ammonium salts and hydrogen bond donors by simple heating. Importantly, these materials are very cheap and can be produced on a large scale.

Given these advantages, the use of DESs in the C–S bond formation could gain much importance in development of sustainable chemistry. Herein, we report the thia-Michael addition employing thiols and α,β-unsaturated compounds in Brønsted acidic deep eutectic solvent under mild conditions. Different acidic DESs have been prepared and employed in this transformation. Quaternary ammonium salt, choline chloride (ChCl), was chosen as the hydrogen bond acceptor, whereas some Brønsted and Lewis acids were tested as the hydrogen bond donors (HBDs). All the DESs were prepared by mixing ChCl with HBDs at 80 °C until a clear solution was formed, which were used without any purification.[18] Phenylmethanethiol **1a** and chalcone **2a** were selected as the model substrates to screen the reaction conditions (Table 1, Scheme 1). The model

Table 1 Optimization of reaction conditions.[a]

Entry	DES (molar ratio)	*T*/°C	*t*/h	Yield of **3a** (%)[b]
1	ChCl/TsOH (1 : 1)	25	3	75
2	ChCl/oxalic acid (1 : 1)	25	3	50
3	ChCl/citric acid (1 : 1)	50	3	32
4	ChCl/malonic acid (1 : 1)	25	3	21
5	ChCl/succinic acid (1 : 1)	25	3	13
6	ChCl/$FeCl_3$ (1 : 1)	25	6	20
7	ChCl/TsOH (1 : 1)	25	3	90[c]

[a] *Reaction conditions*: phenylmethanethiol **1a** (0.36 mmol), chalcone **2a** (0.3 mmol), DES (1 ml). [b] Isolated yields. [c] Methanol (0.5 ml) was added.



1a–e

2a–f

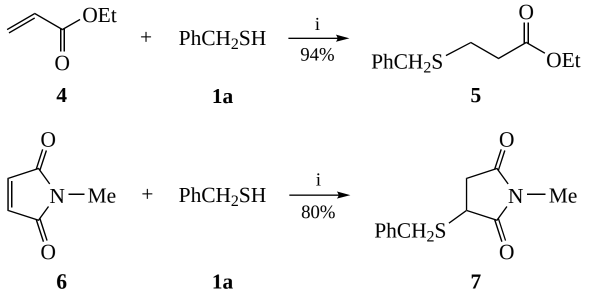
1a $R^1 = PhCH_2$
1b $R^1 = 4\text{-}MeC_6H_4CH_2$
1c $R^1 = 4\text{-}O_2NC_6H_4CH_2$
1d $R^1 = Cy$
1e R^1 = allyl

2a $R^2 = R^3 = Ph$
2b $R^2 = Ph$, $R^3 = Me$
2c R^2 = 2-thienyl, $R^3 = Me$
2d $R^2 = 4\text{-}MeOC_6H_4$, $R^3 = Ph$
2e $R^2 = Ph$, $R^3 = 4\text{-}BrC_6H_4$
2f $R^2 = Ph$, $R^3 = 4\text{-}MeC_6H_4$

3a–i

a $R^1 = PhCH_2$, $R^2 = R^3 = Ph$
b $R^1 = PhCH_2$, $R^2 = Ph$, $R^3 = Me$
c $R^1 = PhCH_2$, R^2 = 2-thienyl, $R^3 = Me$
d $R^1 = 4\text{-}MeC_6H_4CH_2$, $R^2 = Ph$, $R^3 = Me$
e $R^1 = 4\text{-}O_2NC_6H_4CH_2$, $R^2 = Ph$, $R^3 = Me$
f $R^1 = Cy$, $R^2 = Ph$, $R^3 = Me$
g R^1 = allyl, $R^2 = Ph$, $R^3 = Me$
h $R^1 = 4\text{-}O_2NC_6H_4CH_2$, $R^2 = 4\text{-}MeOC_6H_4$, $R^3 = Ph$
i $R^1 = 4\text{-}O_2NC_6H_4CH_2$, $R^2 = Ph$, $R^3 = 4\text{-}BrC_6H_4$

Scheme 1 *Reagents and optimized conditions*: i, thiol **1** (0.36 mmol), α,β-enone **2** (0.3 mmol), ChCl/TsOH (1 ml), methanol (0.5 ml), room temperature, 3 h.



Scheme 2 *Reagents and conditions*: i, **1a** (0.36 mmol), **4** or **6** (0.3 mmol), ChCl / TsOH (1 ml), methanol (0.5 ml), room temperature, 3 h.

reaction in ChCl/TsOH as the DES successfully provided the desired product **3a** in 75% yield (entry 1). Since acid strength of these DESs may affect the reaction, a series of acidic DESs derived from both Brønsted and Lewis acids were then evaluated. Results showed that reactions in ChCl/oxalic acid, ChCl/citric acid, ChCl/malonic acid, ChCl/succinic acid or ChCl/$FeCl_3$ afforded essentially lower yields (entries 2–6). It should be pointed out that a higher reaction temperature (50 °C) was required in ChCl/citric acid due to high viscosity of this system (entry 3). To our delight, the addition of methanol as the co-solvent greatly improved the reaction outcome giving product **3a** in excellent yield (90%, entry 7). We envisioned that methanol additive not only improved the solubility of the substrates but also decreased the viscosity of the reaction medium.

The substrate scope was then explored with a series of thiols and α,β-enones (see Scheme 1).[†] Both electron-withdrawing and electron-donating groups on the benzene ring of arylmethanethiols showed good compatibilities (products **3b** and **3c**). Cyclohexanethiol **1d** and prop-2-ene-1-thiol **1e** gave the corresponding products in good yields. Other chalcones and acetophenones also reacted smoothly to afford the adducts in good yields.

Other α,β-unsaturated carbonyl compounds such as ethyl acrylate **4** and 1-methyl-1*H*-pyrrole-2,5-dione **6** also showed good compatibilities, providing compounds **5** and **7** in 94 and 80% yields, respectively (Scheme 2).

One of the main advantages of this protocol is the DES reuse. In the model reaction **1a** + **2a** → **3a** as an example, once the reaction was finished, the mixture was extracted with EtOAc. The upper organic liquid layer was spilled off with a pipette. The lower layer (DES) was used directly for the next run without any treatment. Recycle studies showed that this process could be repeated up to five consecutive runs with slight loss of yields (90, 90, 87, 84 and 82%, respectively). A plausible reaction mechanism involves the initial protonation of a α,β-unsaturated carbonyl compound. The resulting carbocation would then attack the nucleophilic sulfur atom to form a sulfonium cation followed by the release of a proton to give the final sulfide.

In summary, a 100% atom-efficient thia-Michael addition process between thiols and α,β-unsaturated carbonyl compounds in Brønsted acidic DES at room temperature has been developed. The choline chloride/*p*-toluenesulfonic acidic DES showed good catalytic activity and could be readily recovered and reused.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.030.

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