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Lipase and Deep Eutectic Mixture Catalyzed Efficient Synthesis of Thiazoles in Water at Room Temperature

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Abstract Lipase bio-catalyst or ammonium based deep eutectic mixture efficiently catalyzed aqueous phase synthesis of methyl-thiazole and amino-thiazole derivatives. The simple ammonium deep eutectic catalyst, easily synthesized from choline chloride and urea, is inexpensive, recyclable and bio-degradable, making it suitable for industrial applications.

Keywords Thiazole · Deep eutectic mixtures · Lipase · Phenacyl bromide · Urea

1 Introduction

Thiazole derivatives are found to be associated with several biological activities which has made them extremely useful in the treatment of hypertension [1], schizophrenia [2], inflammation [3], and HIV [4] infections. Its derivatives like aminothiazoles are known to be ligands of estrogen receptors [5] and also adenosine receptor antagonists [6]. Drug formulations containing 2-aminothiazoles are currently available for the treatment of inflammation, breast cancer, HIV-1 and rheumatoid arthritis [7–9]. Among the synthetic methods, Hantzsch synthesis [10] is a direct process involving one-pot condensation of α-haloketones, and thiourea or thioamides in refluxing alcohol.

Since then, many improved methods have been reported for the synthesis of thiazoles using catalyst such as: (a) ammonium-12-molybdophosphate in methanol [11], (b) iodine [12], (c) α-tosyloxyketones with thioureas in PEG-400 [13], (d) Cu(OTf)2-catalyzed coupling of α-diazoketones with thiourea [14], (e) β-cyclodextrin [15]. Although these methods are efficient in terms of yields and some even use greener methods, however, most of these methods hold some demerits which we intend to overcome. The method (a) uses heteropoly acid as an efficient catalyst but uses methanol as solvent whereas method (b) requires overnight heating at 100 °C and method (c) uses larger quantity of PEG-400 (as reaction medium). The method (d) involving diazoketones require toxic metal catalysts in addition to consuming comparatively longer reaction time (2–3 h) and higher temperature (80 °C). The method (e) was greener but no study of recyclability was demonstrated. We have tried to overcome the limitations and retain the benefits of the reported methods by using bio-catalysts or simple deep eutectic mixtures as catalysts in water. Srinivasan and co-workers [16] reported synthesis of amino-thiazoles in aqueous media, but we employ greener catalysts to make this aqueous process even more efficient.

Bio-catalysis is known to be an efficient and green tool for organic synthesis due to its high selectivity and requirement of mild reactions conditions [17]. Lipases are ubiquitous enzymes of considerable physiological importance and industrial potential. Lipases catalyze a number of useful reactions including esterification [18], transesterification [19], regioselective acylation of glycols and menthols [20], and synthesis of peptides [21]. Although the utility of lipases has been observed for various reactions as discussed above, its effectiveness for thiazole synthesis has not yet been explored to the best of our knowledge.

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Thiazole synthesis has also been performed in ionic liquids [22]. However, the ionic liquids based on imidazole and fluorinated anions suffer from the demerits of being toxic and commercially expensive [23]. In this context, deep eutectic mixtures could be a good alternative that include simple eutectic combinations of ammonium salts such as choline chloride with different hydrogen bond donors like urea or lewis acids such as zinc chloride. Choline is a naturally occurring bio-compatible compound and choline chloride is also commercially produced on a large scale as a chicken feed additive whereas urea is found to be present in animal waste product [24]. The deep eutectic solvents would thus be an environmental-friendly and economically viable alternative for conventional catalysts not only on lab scale but also with regard to industrial applications. In the past few years, our research group has focused towards application of deep eutectic mixtures as efficient solvents or catalysts [25–28].

In view of the emerging importance of greener catalysts, we have explored for the first time, the role of lipase catalyst and a deep eutectic mixture, prepared from choline chloride and urea, as efficient and recyclable catalyst in water for synthesis of different thiazole derivatives at room temperature.

2 Experimental

The enzyme lipase was acquired from Sigma Aldrich. It was obtained from *Pseudomonas* sp. strain with particle size of less than 60–100 mesh and activity of 30,000 u g^{-1}. FT–IR spectrums were recorded on a Bomem Hartmann and Braun MB-Series FT–IR spectrometer. ^{1}H NMR spectrums were recorded on Varian 300 MHz mercury plus spectrometer and mass spectral data were obtained with a micromass-Q-TOF (YA105) spectrometer. Common reagent grade chemicals were procured from M/s S.D. Fine Chemical Ltd. India and were used without further purification.

2.1 Preparation of Deep Eutectic Solvent

In this study, two deep eutectic solvents (deep eutectic mixture) were synthesized according to the procedures reported in the literature [29]. The preparation involved reaction of choline chloride **1** (1 mol) with urea **2** (2 mol) at 74 °C (Scheme 1) till a clear solution was obtained which was used for reactions without any purification. This method gives deep eutectic solvent **3** with 100 % atom economy without any other by-product formation.

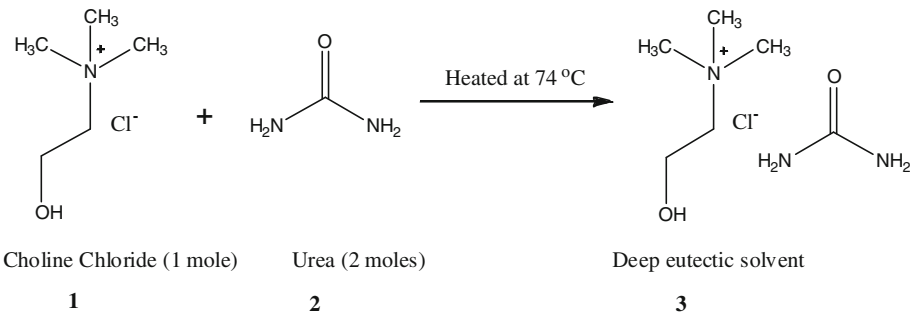
2.2 Typical Procedure for Lipase-Catalyzed Reaction

Phenacyl bromide **4** (R'=H) (1 g, 5.0 mmol) was added to water (10 mL, 10 vol) containing lipase catalyst (100 mg, 10 % by weight of phenacyl bromide derivative) to which thiourea **5** (R=NH_2) (0.40 g, 5.0 mmol) was added. The reaction mixture was stirred in at room temperature under vigorous stirring for 20 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was filtered through a Whatmann No. 42 under suction to remove water. The solid compound on filter paper containing both product and lipase catalyst was added to methanol (7 mL). This solution was then filtered off through a Whatmann No. 42 filter paper to recover the bio-catalyst. The filtrate containing methanol was evaporated under reduced pressure to obtain the crude solid product. The crude product was further purified by column chromatography using toluene as eluent to afford the pure product **6**.

2.3 Typical Procedure for Deep Eutectic Mixture-Catalyzed Reaction

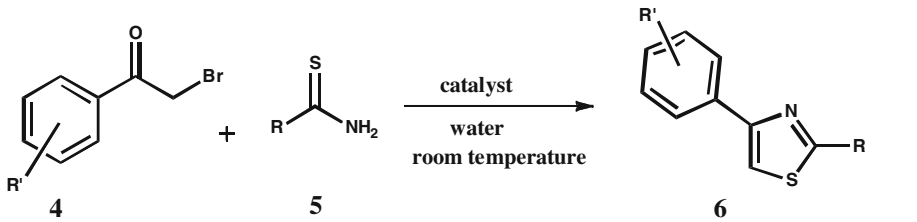
A mixture of phenacyl bromide **4** (R'=H) (1 g, 5.0 mmol) and thiourea **5** (R=NH_2) (0.40 g, 5.0 mmol) was stirred in water (10 mL) containing 20 % deep eutectic mixture catalyst (2 mL) at room temperature under vigorous stirring for 20 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid product was filtered off and the aqueous layer was evaporated under reduced pressure to recover the deep eutectic mixture. The crude product was further purified by column chromatography using toluene as eluent to afford the pure product **6**.

Both the methods were scaled-up to 50 g to obtain 94 % yield in lipase-catalyzed reactions and 95 % yield in deep eutectic mixture catalyzed reactions.



Scheme 1 Preparation of deep eutectic mixture from choline chloride and urea

Scheme 2 Aqueous-phase synthesis of thiazole in presence of deep eutectic mixture/lipase catalyst



where R=NH_2, CH_3, NH-Ph, NH-Ph-OCH_3
R'=H, NO_2, Br, OCH_3

Table 1 Optimization of reaction under different quantities of catalyst in thiazole synthesis from phenacyl bromide with thioamide derivatives

Entry	Solvent	Catalyst	Thiourea yield[a] (%)	Thioacetamide yield[a] (%)
1	H_2O	–	63	55
2	H_2O	5 % DES (ChCl:urea)[b]	82	60
3	H_2O	10 % DES (ChCl:urea)[b]	85	68
4	H_2O	15 % DES (ChCl:urea)[b]	90	80
5	H_2O	20 % DES (ChCl:urea)[b]	95	85
6	H_2O	30 % DES (ChCl:urea)[b]	96	87
7	H_2O	30 % DES (ChCl:glycerol)[b]	67	60
8	H_2O	Lipase (5 % by weight)[c]	89	78
9	H_2O	Lipase (10 % by weight)[c]	94	82
10	H_2O	Lipase (15 % by weight)[c]	95	82

All reactions were carried out with phenacyl bromide (5.0 mmol), thiourea/thioacetamide (5.0 mmol), water (10.0 vol); reaction time: 25 min

[a] Isolated yields of thiazole derivatives

[b] v/v% of DES in water

[c] Percentage by weight of phenacyl bromide

Spectral data for representative compounds.

4-Phenylthiazol-2-amine (**6a**): δH(300 MHz; $CDCl_3$; Me_4Si) 7.76 (s, 1H), 7.32 (s, 2H), 7.19 (m, 5H); ν_{max} cm^{-1} 3437 (N–H Stretch), 3114 (C–H Stretch), 1598 (N–H bend), 1531, 1515 and 1482 (aromatic C–C ring stretch), 1330 (C–N stretch band); Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90; S, 18.19. Found: C, 62.10; H, 4.73; N, 15.41; S, 18.86.

2-Methyl-4-phenylthiazole (**6b**): δH(300 MHz; $CDCl_3$; Me_4Si) 7.30–7.87 (m, 6H), 2.78 (s, 3H); ν_{max} cm^{-1} 3106 (C–H Stretch), 1498 (aromatic C–C ring stretch), 1439 (C=N stretch); Anal. Calcd for $C_{10}H_9NS$: C, 68.53; H, 5.18; N, 7.99; S, 18.30. Found: C, 68.21; H, 4.49; N, 8.22; S, 18.44.

N,4-Diphenylthiazol-2-amine (**6c**): δH(300 MHz; $CDCl_3$; Me_4Si) 7.76–7.19 (m, 10H), 7.06 (s, 1H), 6.72 (s, 1H); ν_{max} cm^{-1} 3300 (N–H Stretch), 2957 (C–H Stretch), 1598 (N–H bend), 1499 (C–C ring stretch), 1314 (C–N stretch band); Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10; S, 12.71. Found: C, 70.45; H, 4.15; N, 10.97; S, 12.30.

N-(4-Methoxyphenyl)-4-phenylthiazol-2-amine (**6d**): δH (300 MHz; $CDCl_3$; Me_4Si) 7.82–6.9 (m, 10H), 6.72 (s, 1H), 3.83 (s, 3H); ν_{max} cm^{-1} 3379 (N–H Stretch), 2837 (C–H Stretch), 1597 (N–H bend), 1556, 1508 and 1480 (aromatic C–C ring stretch) 1324, 1199 (C–N stretch band), 1296 (C–O stretch); Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; O, 5.67; S, 11.36. Found: C, 67.97; H, 4.21; N, 10.06; S, 11.07.

4-(4-Nitrophenyl)thiazol-2-amine (**6e**): δH(300 MHz; $CDCl_3$; Me_4Si) 8.21–8.03 (m, 4H), 7.39 (s, 1H), 7.21 (s, 2H); ν_{max} cm^{-1} 3396 (N–H Stretch), 3114 (C–H Stretch), 1591 (N–H bend), 1536, 1319 (N–O stretch), 1640, 1482 (aromatic C–C ring stretch), 1410, 1108 (C–N stretch band); Anal. Calcd for $C_9H_7N_3O_2S$: C, 48.86; H, 3.19; N, 18.99; O, 14.46; S, 14.49. Found: C, 47.77; H, 2.25; N, 17.24; S, 14.45.

3 Results and Discussion

The reaction for synthesis of thiazole from phenacyl bromide and thioamide derivatives (Scheme 2) was initially optimized for deciding the amount of lipase or deep eutectic mixture catalyst. In case of lipase-catalyzed reactions, 10 % lipase by weight of phenacyl bromide was found to give the best results. It could also be observed from Table 1 that 20 and 30 % deep eutectic mixture catalyst (v/v% of deep eutectic mixture in water) gave almost

Table 2 Thiazole synthesis from phenacyl bromide or its derivatives with thioamide derivatives in water in presence of DES or lipase as catalyst

Entry	Ar	R	Reaction time (in min)	Deep eutectic mixture catalyst[a]	Lipase catalyst[b]	Melting point	
				Yield[c] (%)	Yield[c] (%)	Found	Literature
6a	Ph–	$–NH_2$	20	95 (Reported method = 53 %) [30]	94	150	150–151 [30]
6b	Ph–	$–CH_3$	25	85 (Reported method = 86 % in 1.5 h) [15]	82	66	67 [31]
6c	Ph–	–NHPh	20	96 (Reported method = 78 %) [30]	95	134–136	136–137 [30]
6d	Ph–	$–NH–C_6H_4$-4-OMe	20	98 (Reported method = 96 % in 15 min) [33]	97	160–162	163 [33]
6e	4-$NO_2–C_6H_4$–	$–NH_2$	20	95 (Reported method = 99 %, overnight heating) [32]	95	284–286	285–286 [32]
6f	4-$NO_2–C_6H_4$–	$–CH_3$	25	87 (Reported method = 95 % in 5 min) [36]	82	144–146	145 [31]
6g	4-$NO_2–C_6H_4$–	–NHPh	20	97 (Reported method = quantitative yield, in 5 min) [34]	95	220	226–229 [34]
6h	4-NO_2-C_6H_4–	$–NH–C_6H_4$-4-OMe	15	94	91	166–168	–
6i	4-Br–C_6H_4–	–NHPh	20	93 (Reported method = 87 % in 7 h) [35]	91	144–146	143–144 [35]
6j	4-Br–C_6H_4–	$–NH–C_6H_4$-4-OMe	15	94	93	196–198	–
6k	4-MeO–C_6H_4	$–CH_3$	25	81 (Reported method = 97 %, overnight heating) [32]	80	64	67–69 [36]
6l	4-MeO–C_6H_4	$–NH–C_6H_4$-4-OMe	20	91	90	178–180	–

All reactions were carried out with phenacyl bromide derivatives **4** (5.0 mmol), thioamide derivatives **5** (5.0 mmol), water (10.0 vol), room temperature

[a] Reaction at room temperature; 20 % DES in water (v/v% of DES in water)

[b] Reaction at room temperature; 10 % lipase by weight of phenacyl bromide derivative

[c] Isolated yields of thiazole derivatives

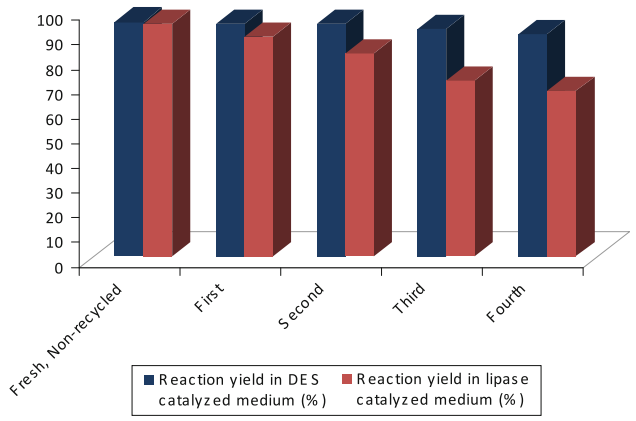


Fig. 1 Recycling studies of DES and lipase catalyst in thiazole synthesis from phenacyl bromide and thiourea

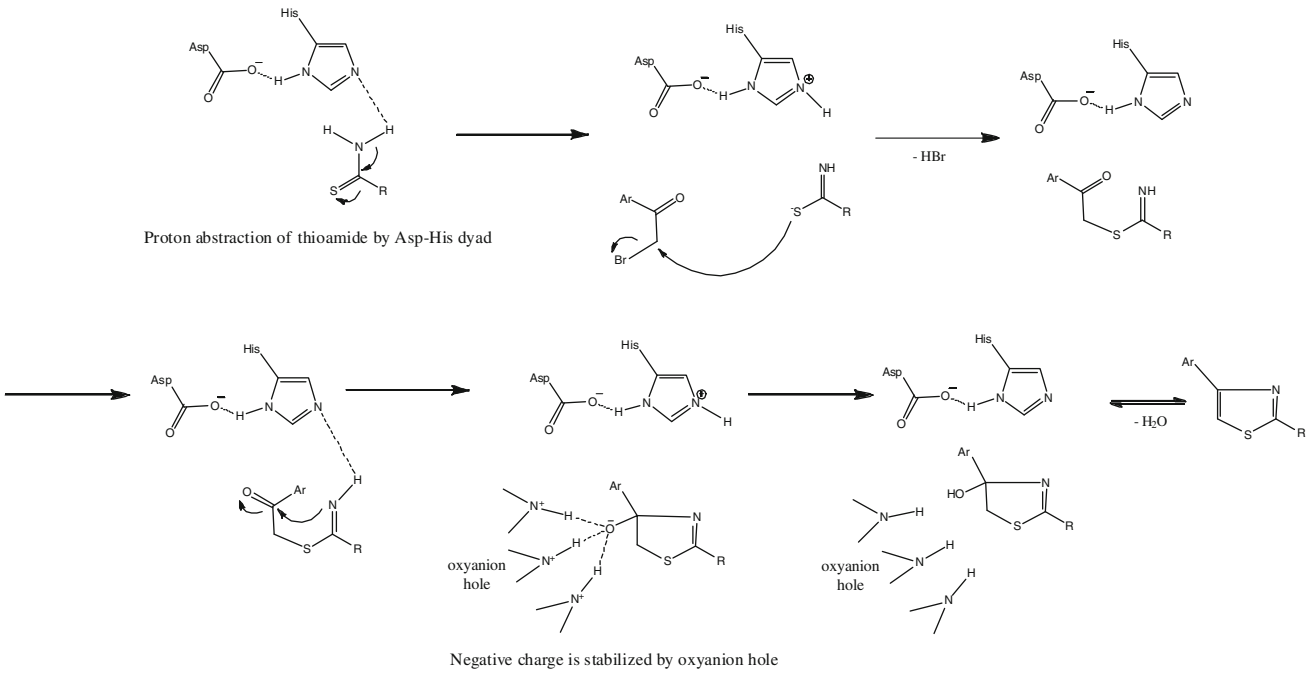
similar results. Hence, the quantity of deep eutectic mixture was optimized to 20 %. Thus, the addition of catalysts (lipase or deep eutectic mixture) improved the yields in comparison to reaction in water.

A variety of amino and methylthiazole derivatives were synthesized in water in presence of two bio-degradable catalysts including lipase or deep eutectic mixtures as summarized in Table 2. The reaction conditions were mild (room temperature) and the products were obtained within much shorter times and in excellent yields thus giving improved results as compared to previous procedures reported in water.

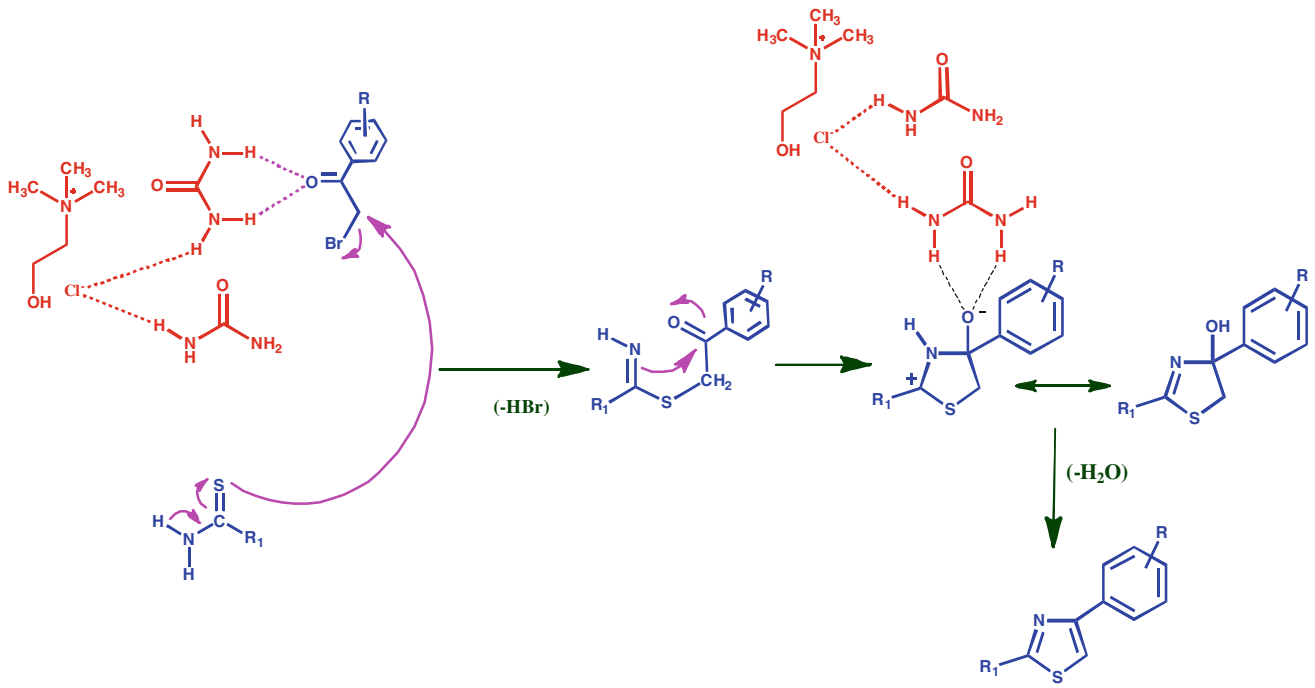
The recycling of lipase and deep eutectic mixture catalysts were studied up to four runs considering the aminothiazole synthesis from phenacyl bromide and thiourea as the standard reaction. The results of recycling studies are summarized in Fig. 1. It could be observed that both the catalysts can be recycled efficiently at least up to four times with lipase showing reduction in activity after second run whereas deep eutectic mixture gives quite high yields even after four runs. However, the color of DES gets slightly darkened after each run.

In lipase-catalyzed reaction, methanol was added for solubilizing the product that would enable the separation of lipase catalyst. The methanol was recovered by distillation of the filtrate under vacuum. This process also uses only methanol which is greener than many organic volatile solvents. In deep eutectic mixture-catalyzed reaction, the reaction mass was simply filtered through a filter paper to obtain crude solid product where the deep eutectic catalyst could be recovered in case of scale-up batches by removing water under vacuum from the filtrate. The work-up, thus, did not involve any volatile organic solvent and is completely eco-friendly in nature.

Although the mechanism illustrating the role of such deep eutectic solvents or lipase catalyst in thiazole synthesis is yet to be confirmed, we suggest a mechanism predicting their probable role in synthesis. In case of lipase catalyst, the imidazole ring of the Asp-His dyad present in lipase catalyst could abstract a proton from the thioamide moiety thus enabling its attack on the phenacyl bromide



Scheme 3 Proposed mechanism for thiazole synthesis in lipase-catalyzed medium



Scheme 4 Proposed mechanism for thiazole synthesis in deep eutectic mixture-catalyzed medium

derivative as shown in Scheme 3. The negative charge developed on oxygen atom during cyclization step is further stabilized by the oxyanion hole.

In case of deep eutectic mixture catalyzed reaction, the urea component is well known for its hydrogen bonding ability [37] which may assist in enhancing the electrophilicity of methylene group in phenacyl bromide as well as may stabilize the oxygen anion formed after cyclization step as shown in Scheme 4.

4 Conclusions

In summary, we have developed a simple, green and efficient catalytic system using lipase or deep eutectic mixtures for synthesis of various methyl thiazoles and aminothiazole derivatives in aqueous medium. The reaction gave excellent yields in very short reaction times. Both the catalysts are biodegradable, non-toxic and were successfully recycled and reused. In addition, the process of preparing deep eutectic mixture is very simple and requires inexpensive starting materials. The present method eliminates the need of hazardous organic solvents and toxic/expensive catalysts. Moreover, the scale-up batch and recycling possibility widens the scope of industrial applicability of this method.

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