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Visible light triggered, catalyst free approach for the synthesis of thiazoles and imidazo[2,1-b]thiazoles in EtOH : H_2O green medium

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Abstract :

The development of a visible light promoted, mild and greener approach for the synthesis of highly functionalized thiazoles and imidazo[2, 1-b]thiazoles under photochemical activation in EtOH:H_2O green medium is demonstrated. The characteristic feature of the present protocol is the utilization of visible light (an omnipresent, nontoxic, environmentally benign and inexpensive reagent) to form C-S, C-N bond and circumlocute the use of catalysts or photosensitizers. The reported protocol is the first example of visible light promoted synthesis of thiazoles and imidazo[2, 1-b]thiazoles with various attractive features like being catalyst free, eco-efficient and possessing cost effectiveness, short reaction time, excellent yields and the sustainability to fulfill the parameters of green chemistry.

Introduction

Increasing needs are the key to new inventions which lead to new thoughts and new creations. The frequent use of hazardous solvents and metal catalysts in the laboratory pollutes our environment severely. Researchers and scientists are thus shifting their focus towards maximum environmentally benign and sustainable utilization of resources which is capable of being maintained at a steady level without causing ecological damage or exhausting natural resources.[1] The development of visible light mediated synthesis has been recognised as a prominent route for a number of organic transformations[2] because of its ability to provide activation energy to the reactant in the chemical reactions. Light is an abundant, easily handled, renewable energy source as well as a valuable tool for a myriad of green chemical reactions and thus has attracted much attention.[3] Chemists have successfully performed a variety of visible light induced reactions and

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achieved their goals. Several research groups have used compact fluorescent light (CFL) and light emmiting diodes (LEDs) as a visible light source for the formation of the target compound. Easy availability, simple handling, cost effectiveness and safe approach, places this method under the heading of green chemistry.[4]

There are several organic molecules which are unable to absorb visible light.[5] To overcome this barrier chemists use photo sensitizers and photo catalysts. In literature different methods have been reported which incorporate the transition metals, certain organic dyes and nanoparticles as a photocatalyst.[6] However a number of disadvantages associated with trasition metal photocatalyst as it shows adverse inherent malignancy, short durability and expensiveness.[7] At present, many nanoparticles like ZnO/γ-Mn_2O_3,[8a] ZnO/CdO,[8b] ZnO/V_2O_5,[8c] ZnO/Ag/Mn_2O_3[8d] and electrospun nanomaterials[8e] which also act as photocatalytic substances and fruitful for degradation of several textile elluent, organic dyes and organic pollutants. But still nanoparticles exhibit drawbacks as large band gap,[8f] depletion of crystallinity[8g] which consequence less efficiency. Within this context a catalyst free synthesis using green solvent medium in various synthetic processes has emerged as an important tool.[9]

Thiazole and its derivatives are present in innumerable natural compounds such as in epithilone, thiostrepton, TPP (a coenzyme of Krebs cycle), carboxylase vitamin B1 and antibiotics (penicillin),[10] with significant medicinal and biological importance. Thiazoles are largely associated with medicinal chemistry exhibiting vast applications in drug development for the treatment of allergies,[11] inflammation,[12] HIV infections,[13] hypertension,[14] bacterial infections,[15] hypnotics,[16] schizophrenia[17] and treatment of pain,[18] as new inhibitors of bacterial DNA gyrase B[19] and as fibrinogen receptor antagonists with antithrombotic activity.[20] They express tremendous biological activities such as being antitumor,[21] antifungal,[22] antimicrobial,[23] anti-inflammatory,[24] antitubercular,[25] anticonvulsant,[26] diuretic,[27] neuroprotective and having antioxidant activity.[28]

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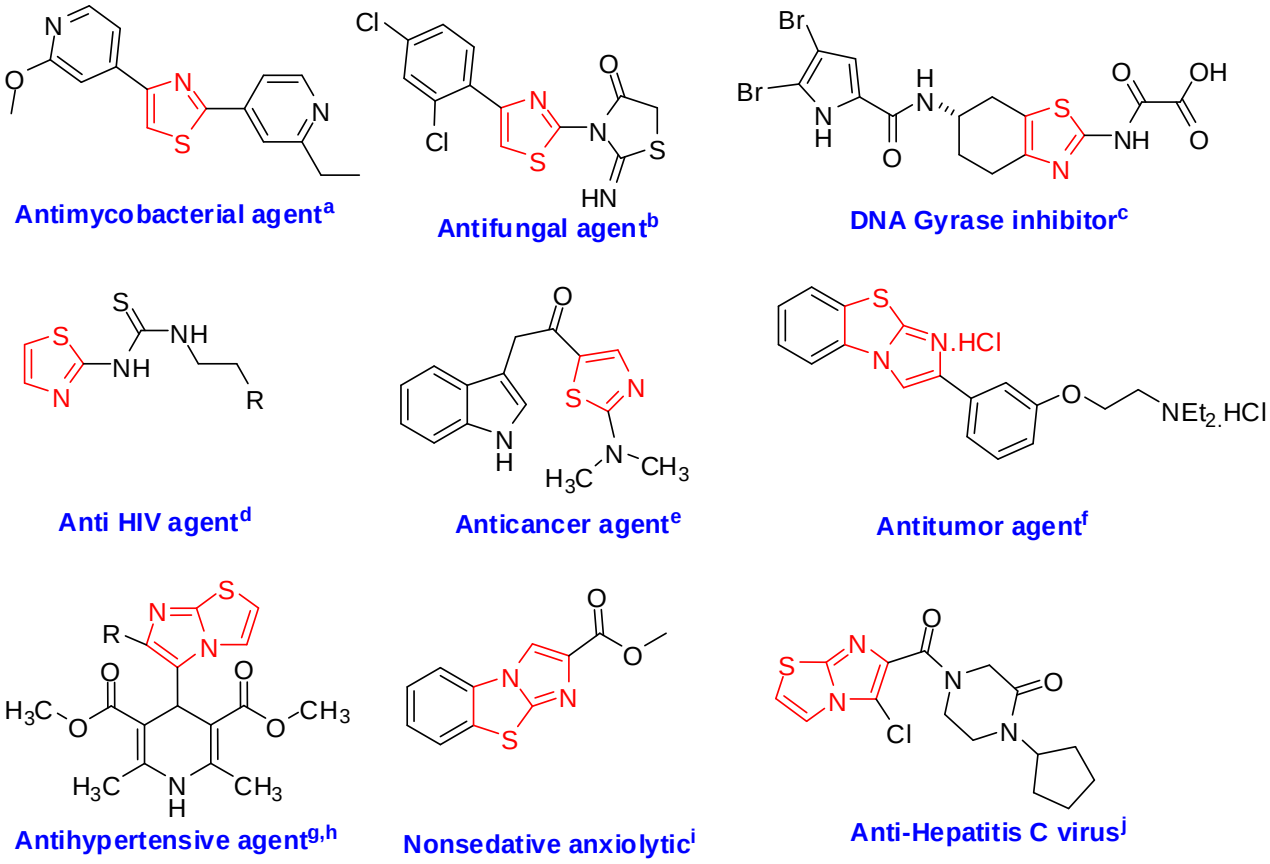

Figure[29a-j] Some medicinally important derivatives of thiazole and imidazothiazole

Numerous protocols for the synthesis of thiazoles[30] and imidazothiazoles[31] using various types of catalysts and different reaction conditions have been developed. Though the reported methods have several advantages, there are certain drawbacks associated with these methods example long reaction time, use of costly catalyst, difficulty in the recovery of high boiling solvent, low yield of the product, limited availability of starting material, non-reusability of catalyst and solvent. Thus there was a need to design a more eco-efficient method for the synthesis of thiazoles. In continuation of our previous work,[32] we were encouraged to develop a more sustainable process for the synthesis of the target scaffold which involved a visible light induced reaction without the use of a catalyst for the completion of the reaction. Mild reaction conditions make it a more relevant, efficient and a cleaner methodology for the synthesis of the target scaffold. (**Scheme 1)**

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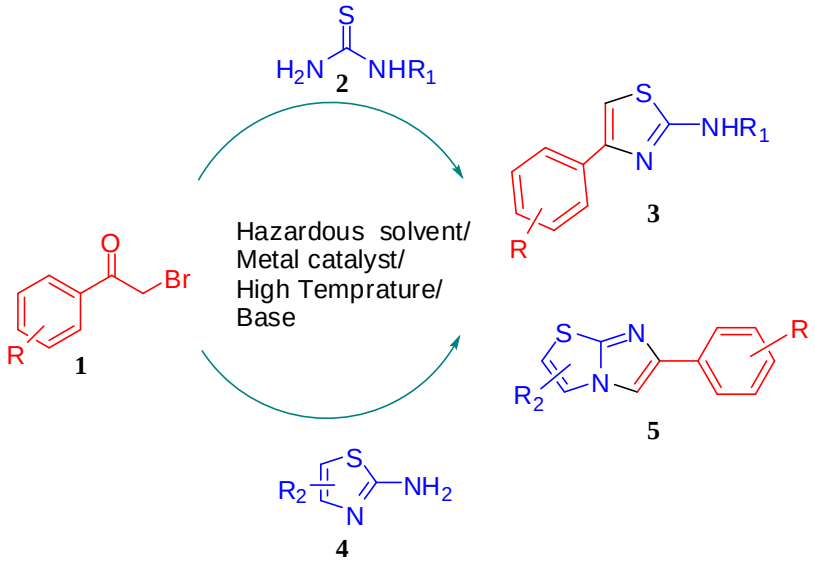
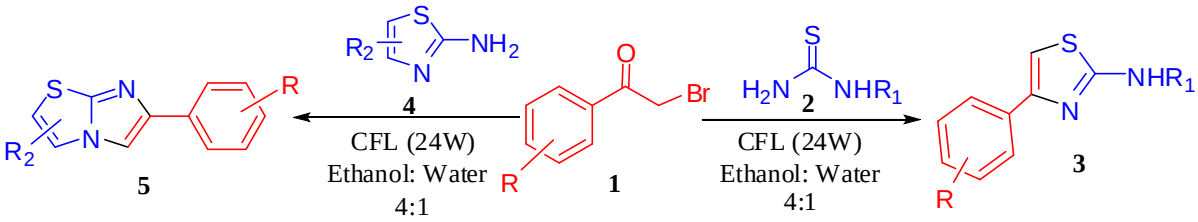
Previous works :



Present work :



Scheme 1 Synthesis of thiazole (3a) & (5a) derivatives

For optimization studies of visible light mediated two component synthesis of thiazoles and imidazothiazoles, we carried out two different sets of reactions by the use of phenacyl bromide (**1**), N-phenylthiourea (**2**) and 2-aminothiazole (**4**) as reactants. Condensation of phenacyl bromide (**1**, 1mmol) and N-phenylthiourea (**2**, 1mmol) and condensation of phenacyl bromide (**1**, 1mmol) and 2-aminothiazole (**4**, 1mmol) have been taken as model reactions for the synthesis of different types of thiazoles. During optimization we examined the effect of different solvents, different intensities of light sources and varied catalysts under different experimental conditions to obtain the best condition for the above transformation (Table 1). In our initial endeavour, we took two reaction mixtures with 1.0 mmol of each reactant in ethanol using CFL (24W)

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irradiation as a source of visible light. Under this condition, the condensation of phenacyl bromide (**1**) and N-phenyl thiourea (**2**) gave the product (**3a**) with 85% yield within 10 minutes and condensation of phenacyl bromide (**1**) and 2-aminothiazole (**4)** afforded the product (**5a**) with 55% yield within 5 h (Table 1, entry 8). An interesting result was obtained by the condensation of (**1**) and (**2**). Immediate formation of product (**3**) took place on addition of second reactant, confirmed by TLC analysis but pure product was formed after 10 minutes. When the same model reactions were performed under catalyst free conditions in a variety of other non-polar traditional organic solvents at rt, they resulted in lower yield of the product. In case of DCM and THF the reaction mixture showed the non-consumption of the starting reactant materials on TLC and resulted in moderate yield of the product (**3a**). However, product (**5a**) was not formed in case of DCM within 5h (Table 1, entry 4) and took almost 24 h of CFL irradiation and resulted in trace amount of product (**5a**); in case of THF product (**5a**) afforded very poor yield of the product (Table 1, entry 2). In case of toluene there was a solubility concern of reactant (**2**) and that's why it afforded a very low, 15% yield of product (**3a**). However product (**5a**) was not formed within 5h and took almost 24 h of CFL irradiation to get the trace amount of the product (**5a**). In order to increase the yield of the product we next performed our synthesis in polar solvents like methanol and ethanol. Interestingly there occurred an increase in yield of the product (**3a**) and (**5a**). Now our complete focus on further improvement of the reaction with respect to time. When we used methanol a small amount of phenacyl bromide (**1**) and N-phenyl thiourea (**2**) remained unutilized after 10 minutes resulted 80% yield of the product (Table 1, entries 7), moreover the pure product (**3a**) was formed after 1 h with 90% yield; while in case of ethanol, a considerable decrease in reaction time was observed and pure product was formed with 85% yield (Table 1, entries 8) within 10 minutes. After that we tried mixed solvent system of EtOH : H_2O to carry out the above transformation and found that EtOH : H_2O solvent system proved successful in increasing the yield of the product (Table 1, entries 9,10,11,12). The utility of ethanol and water is to increase the solubility of reactants and in turn, the yield of the product. It is also hypothesized that the transition states of the above reaction would be stabilized by water because of its high static permittivity.[33] The increased yield of product in EtOH:H_2O solvent system may be due to the hydrophobic nature of reactant (**1**) and (**4**) in water. This leads to an increase in the number of collisions between reactants and results in increasing their ground state energy as well as the

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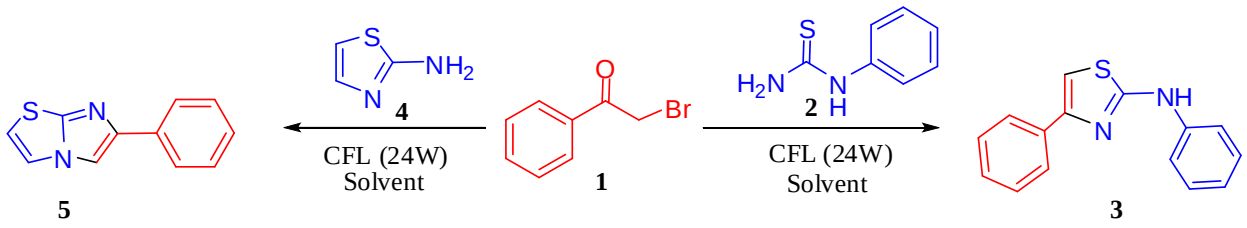
reaction rates. In order to further increase the efficiency of the reaction we used different ratio of EtOH : H_2O solvent system and discovered that (4:1) combination gives the best result (Table 1, entries 12). At this stage, in quest of eco-friendlier conditions, both the test reactions were carried out in neat condition without the use of a catalyst.[34] No reaction was observed (Table 1, entries 13). A catalyst free synthesis using EtOH : H_2O (**4:1**) as a solvent is a considerably cost effective, safer and environmentally benign method for the above transformation.

Table 1 optimization table of solvent[a]



Entry	Solvent	Time (min)	Yield[b] (3a)	Time (h)	Yield[b] (5a)
1	Toluene	10	15	5	-[c]
2	THF	10	65	5	15
3	Benzene	10	50	5	-[c]
4	DCM	10	73	5	-[c]
5	DMSO	10	75	5	28
6	CH_3CN	10	77	5	Trace
7	Methanol	10	80	5	45
8	EtOH	10	85	5	55
9	EtOH:H_2O(1:1)	10	86	5	55
10	EtOH:H_2O(2:1)	10	86	5	57
11	EtOH:H_2O(3:1)	10	93	5	59
12	EtOH:H_2O(4:1)	10	95	5	60
13	Neat	10	-[c]	5	-[c]

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol) in solvent were irradiated under open air at room temperature using CFL (24W). [b]Isolated yield of the product (%). [c]not detected.

After the realisation of the best solvent system for the synthesis of thiazoles, we investigated different sources and intensities of visible light irradiation by performing a series of reactions

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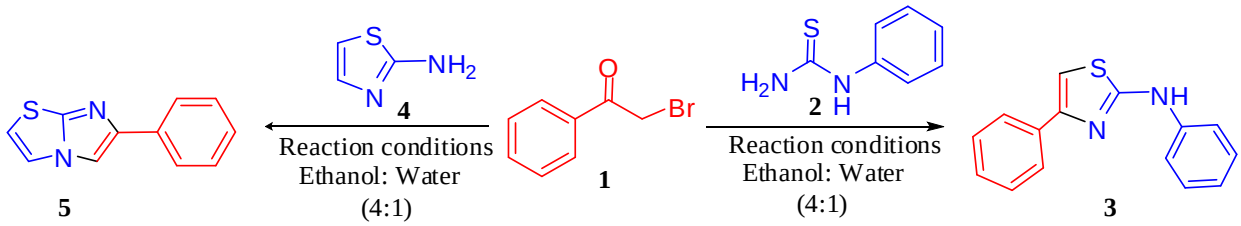
using CFL light (18W and 20W) and LEDs (white 7W). It was found that when we performed the reaction in compact fluorescent lamp (CFL, 24W) in place of LEDs, the product formed readily (Table 2, entry 1,8). However in the absence of visible light, the rate of formation of product significantly decreases (Table 2, entry 2, 3). We further performed our test reaction with photoredox catalyst, eosin Y which is activated by irradiating visible light. It was seen that although the reaction initially completed a bit faster with 0.5mol% and 1mol% of eosin Y, but the difference in final yield of the product was marginal (Table 2, entries 1, 9 and 10). Therefore we selected a catalyst free condition for the required transformation. The presence of oxygen as an oxidant was important for the formation of the desired product since the product was formed in traces in the absence of oxygen (Table 2, entries 4, 5). Moreover, the reaction was inhibited with benzoquinone (**2** mmol) (Table 2, entry 11) in optimized state, which indicates that there may be radical intermediates involved in the reaction.[35]

Table 2 optimization table of reaction conditions[a]



Entry	Reaction Condition	Time (min)	Yield[b] (3a)	Time (h)	Yield[b] (5a)
1	24W, CFL, air, no catalyst	10	95	5	60
2	Daylight, air, no catalyst	10	43	5	18
3	No light, air, no catalyst	10	34	5	10
4	CFL , degassed	10	54	5	-[c]
5	CFL , N_2	10	36	5	-[c]
6	20W, CFL, air, no catalyst	10	87	5	52
7	18 W, CFL, air, no catalyst	10	80	5	40
8	White LED (7W), no catalyst	10	76	5	23
9	CFL, air, eosinY (0.5 mol%)	10	96	5	60

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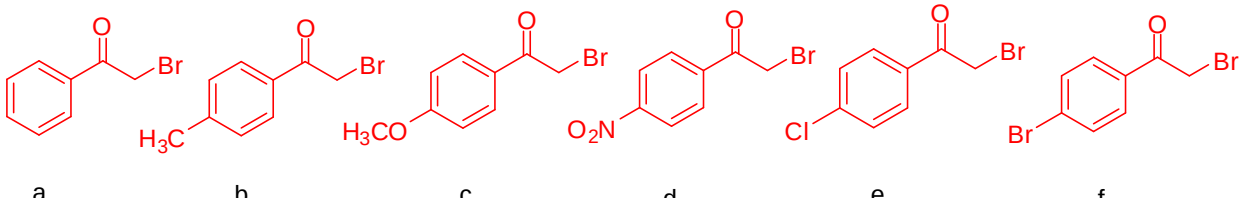
10	CFL , air, eosin Y(1mol%)	10	96	5	60
11	CFL. Air, Benzoquinone[d]	10	52	5	16

[a]Reaction condition: **1a** (1.0 mmol), **2a** (1.0 mmol)) in ethanol: water irradiated using CFL under open air at room temperature. [b]Isolated yield of the product (%).[c]not detected. [d]2 mmol.

Once the optimal conditions had been finalised the scope and limitations of the developed synthetic strategy was explored by the use of a series of different derivatives of phenacyl bromides (**1**), thiourea (**2**) and thiazoles (**4**). It was observed that the use of phenacyl bromide **(1)** bearing an electron withdrawing group showed a significant effect on the yield of the product. Similarly, use of thiourea with or without phenyl ring affected the yield of the product; thiourea bearing phenyl ring as a substituent increases the yield of the product, the product being free from the need of purification. In case of thiourea purification is necessary to obtain the pure product and the yield of the product also is less as compared to that in the case of N-phenyl thiourea.

Different types of phenacyl bromide used (**1**)



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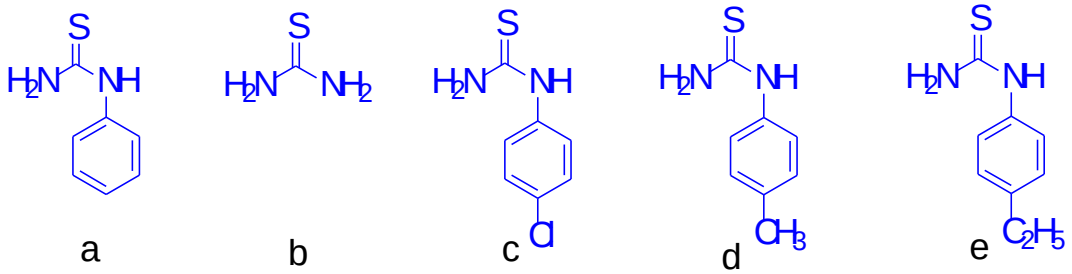
Different types of thiourea used (**2**)-



a b c d e

Different types of thiazoles used (**4**)-

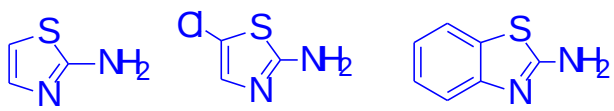


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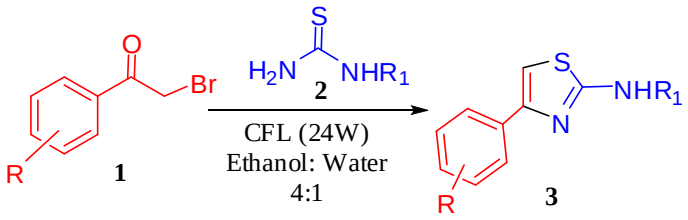
Table 3 Substrate scope[a] (3)



Entry	Phenacyl bromide (**1**)	Thiourea (**2**)	Product (**3**)	Time (min)	Yield[b] (%)
1	a	a	3aa	08	95
2	a	b	3ab	10	88
3	b	a	3ba	10	85
4	b	d	3bd	10	82
5	b	b	3bb	10	82
6	c	a	3ca	09	87
7	c	b	3cb	09	85
8	d	a	3da	05	96
9	d	b	3db	05	94
10	e	a	3ea	07	94
11	e	c	3ec	07	94
12	e	b	3eb	09	90
13	f	a	3fa	09	89
14	f	b	3fb	10	87
15	f	c	3fc	08	89
16	a	e	3ae	10	81

[a]All reactions were carried out in EtOH: H_2O (4:1) in the prescence of visible light irradiation using a 24W CFL at room temperature under air. [b]Isolated yield of the product (%).

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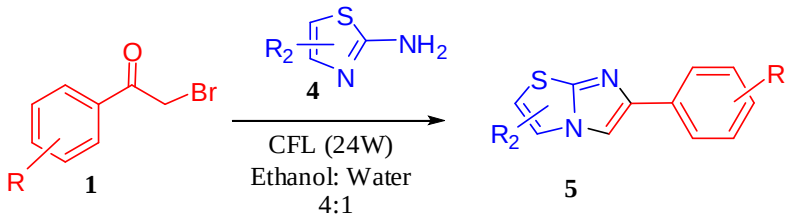
Table 4 Substrate scope[a] (5)



Entry	Phenacyl bromide (**1**)	2-aminothiazole (**4**)	Product (**5**)	Time (h)	Yield[b] (%)
1	a	a	5aa	5.0	60
2	f	b	5fb	5.5	59
3	d	b	5db	5.0	61
4	g	b	5gb	6.5	50
5	a	c	5ac	6.5	53
6	c	c	5cc	6.5	55
7	e	c	5ec	6.5	53

[a]All reactions were carried out in EtOH: H_2O (4:1) in the prescence of visible light irradiation using a 24W CFL at room temperature under air. [b]Isolated yield of the product (%).

Mechanism

On the basis of literature surey,[36, 37, 38] a plausible mechanistic pathway for the synthesis of different types of thiazoles has been proposed. The reaction was initiated by [1,3]tautomerism in reactants (2) and (4). Then visible light promoted homolytic fission of the C-Br bond of phenacyl bromide, S-H bond of N-phenyl thiourea (Scheme 2) and N-H bond of 2-amino thiazole (Scheme 3) takes place resulting to free radicals (A), (B), (C) respectively. After that radical (A) combines with (B) (Scheme 2) and radical (A) combines with (C) (Scheme 3) to give (D) and (E), respectively as mentioned in the mechanism. A homolytic cleavage of carbonyl carbon supported by hydrogen free radical and similar cleavage of N-H bond supported by bromine free radical takes place. Finally the newly formed free radicals (F) and (G) coalesce to form the desired product (**3)** and (**5)** via cyclization followed by removal of H_2O molecule.

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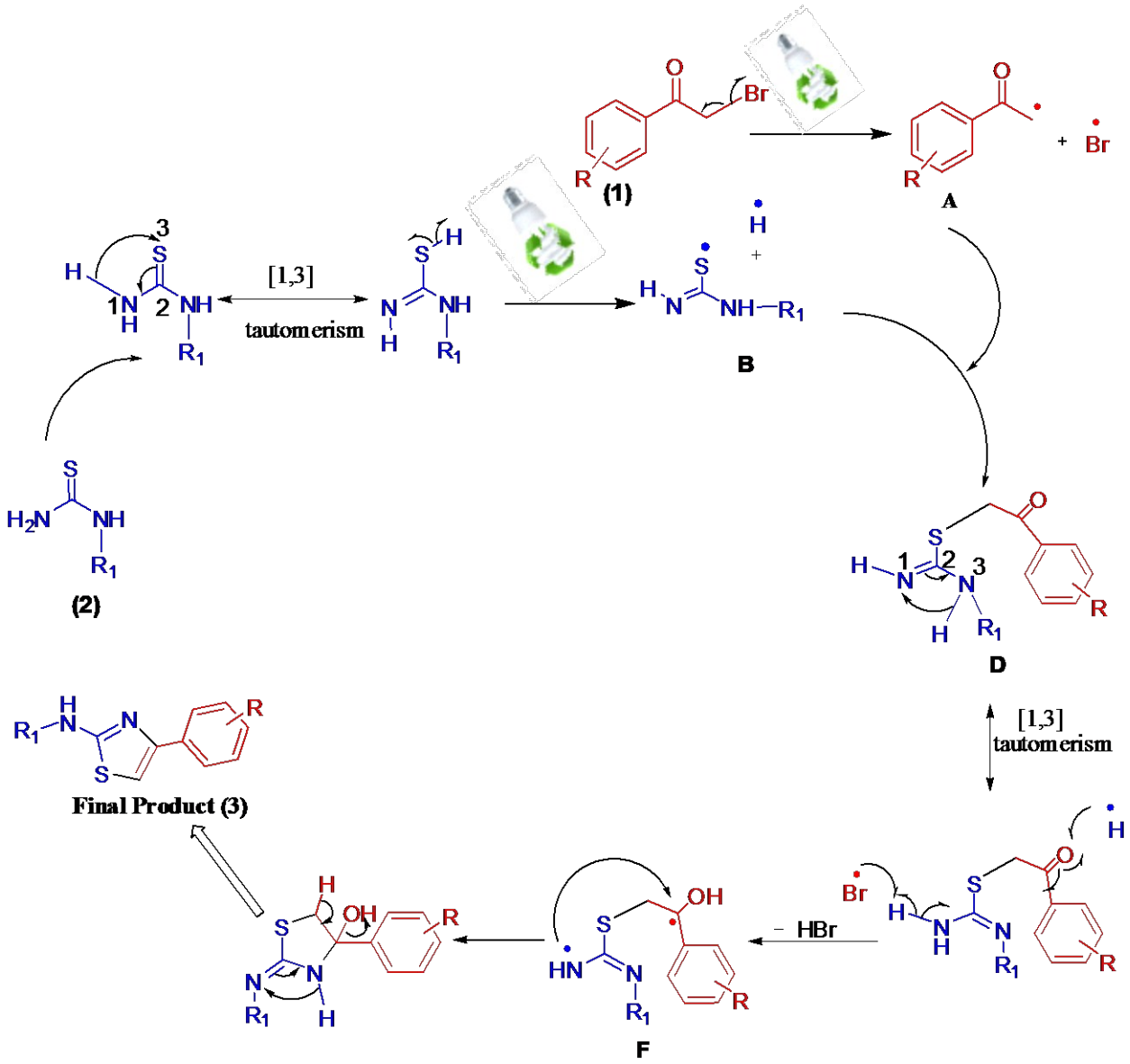

Scheme 2 Plausible mechanism for the synthesis of thiazole derivatives

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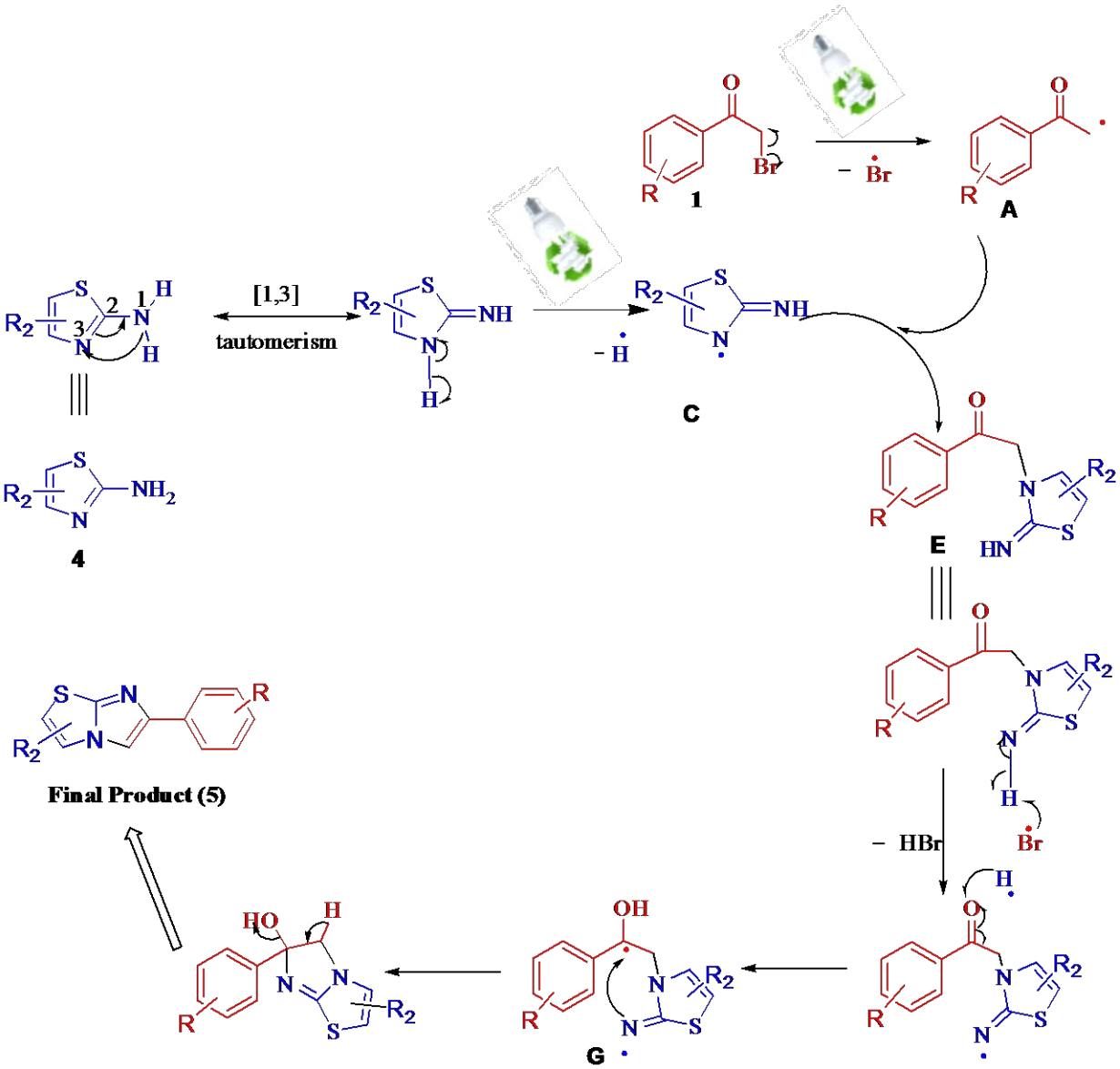

Scheme 3 Plausible mechanism for the synthesis of imidazo[2,1-b]thiazole derivatives

Conclusion

In summary, we have disclosed a visible-light-induced synthetic strategy to attain a facile synthesis of biologically and medicinally important thiazoles (**3**) and imidazo-thiazoles (**5**) via oxidative coupling of phenacyl bromide (**1**) with N-phenyl thiourea (**2**) and 2-amino thiazole (**4**) without the use of heat, base, ligands or an additional oxidant. The present protocol has been applied to the rapid synthesis of products (**3**) and (**5**) using commercially available substrates,

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without the use of hazardous chemicals, catalysts or harsh reaction conditions. The extension of methodology can be examined with a variety of phenacyl bromide derivatives as well as with thiourea and 2-amino thiazole derivatives. Utilization of visible light, eco-efficiency, cost-effectiveness, use of greener reagent, no requirement of bases and catalysts, use of mixed solvent system of EtOH:H_2O, experimental feasibility, short reaction time, easy workup and high yields of the product makes this protocol attractive and superior to the proposed other methods.

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Abstract

The development of a visible light promoted, mild and greener approach for the synthesis of highly functionalized thiazoles and imidazo[2, 1-b]thiazoles under photochemical activation in EtOH:H_2O green medium is demonstrated. The characteristic feature of the present protocol is the utilization of visible light (an omnipresent, nontoxic, environmentally benign and inexpensive reagent) to form C-S, C-N bond and circumlocute the use of catalysts or photo sensitizers. The reported protocol is the first example of visible light promoted synthesis of thiazoles and imidazo[2, 1-b]thiazoles with various attractive features like being catalyst free, eco-efficient and possessing cost effectiveness, short reaction time, excellent yields and the sustainability to fulfill the parameters of green chemistry.