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Visible Light-Mediated Coupling of Thioureas and 1,3-Dicarbonyls: Towards a Leaving Group-Free Synthesis of Aminothiazoles

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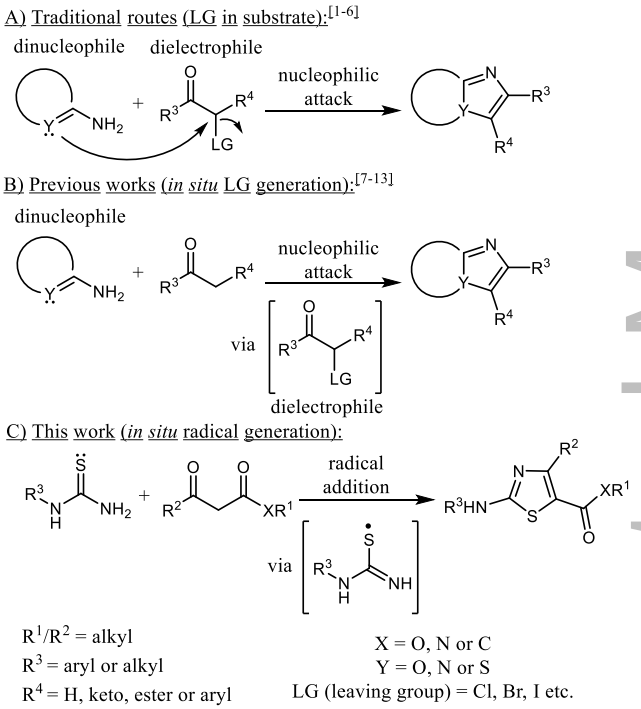
Abstract. A synthesis of aminothiazoles from various 1,3-dicarbonyls and thioureas without a leaving group has been developed. The reaction is photocatalyzed by tetraiodofluorescein, an organic dye. Under irradiation with green LEDs, a sulfur radical is generated *in situ* from thiourea, followed by addition to the enol tautomer, forming the aminothiazole backbone. This novel strategy provides a greener alternative to the traditional leaving group protocols, with excellent atom economy.

Keywords: Photocatalysis; Radicals; Green chemistry; Heterocycles; Cyclization

The traditional method of coupling α-halo 1,3-dicarbonyls or α-halo acetophenones with various dinucleophiles is a popular protocol used in the synthesis of a wide array of heteroaromatic backbones including imidazo[1,2-*a*]pyridines,[1] thiazoles,[2] oxazoles[3] and (benzo[*d*])imidazo[2,1-*b*]-thiazoles[4] (Scheme 1A). A leaving group at the *α*-carbon of the 1,3-dicarbonyls or acetophenones is necessary to switch the polarity of the *α*-carbon from nucleophilic to electrophilic and also to direct the nucleophilic attack by the respective dinucleophilic coupling partners.

As most of the α-halo 1,3-dicarbonyls and acetophenones are not commercially available and thus require prior prefunctionalization, it is not surprising that recent protocols have employed *in situ* α-halogenation strategies for the synthesis of the aforementioned heteroaromatics (Scheme 1B). These protocols use various halogenating reagents including *N*-bromo and iodosuccinimide (NBS and NIS),[5] CBr_4,[6] molecular iodine,[7] tetra *n*-butylammonium iodide (TBAI),[8] metal halides[9] and hypervalent iodine compounds.[10] We have previously applied an *in situ* α-halogenation strategy in the synthesis of



Scheme 1. Existing strategies for heteroaromatic synthesis via coupling of dinucleophiles and *α*-halo dielectrophiles and proposed leaving group-free protocol.

imidazo[1,2-*a*]pyridines and thiazoles using $CBrCl_3$ as the α-brominating agent.[11]

It is known that in the presence of $Mn(OAc)_3$,[12] peroxides and/or I_2, radicals can form at the α-carbon of 1,3-dicarbonyls[13] and undergo radical addition with unsaturated alkyne or alkene moieties.[14] We wanted to investigate if it is possible to reverse the roles, with a thiol radical formed *in situ* from thiourea undergoing a radical addition with the enol tautomer of 1,3-dicarbonyls instead. This will allow the

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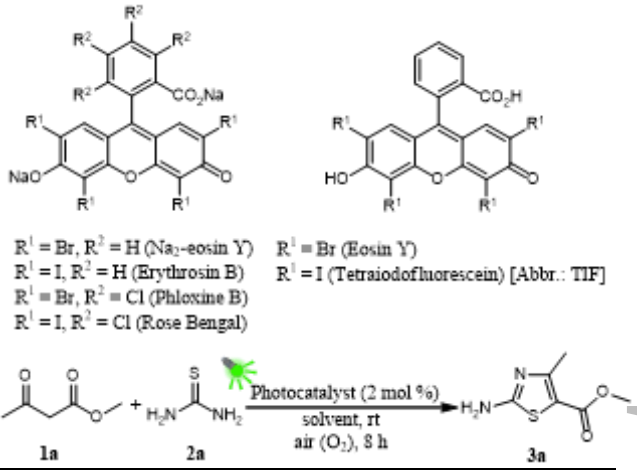
synthesis of aminothiazoles from the coupling of 1,3-dicarbonyls and thiourea without the need of a leaving group (Scheme 1C), a superior strategy to that of traditional and *in situ* halogenation protocols.

Yadav's group reported that a thiol radical could be formed *in situ* from thiobenzamide under visible light using eosin Y as a photosensitizer.[15] Eosin Y belongs to a group of organic dyes known as fluorescein.[16] Eosin Y and its fluorescein derivatives eosin B, Rose Bengal, and erythrosin B are attractive photoredox catalyst options because they are cheap, commercially available, and are often considered to be less toxic and more environmentally benign compared to transition metal photocatalysts.[17] In recent years, these fluorescein-based photocatalysts have been used in a wide range of photoredox reactions,[18] including the synthesis of heterocycles such as 1,2,4 thiadiazoles,[15] benzothiophenes,[19] pyrroloindolines,[20] coumarins,[21] benzofurans,[22] phenanthridines,[23] pyrroloisoquinolines[24] and quinazolinones.[25]

The aminothiazole backbone is widely found in natural products, pharmaceuticals, and agro-chemicals.[26] It is present in compounds possessing diverse and important medicinal and biological properties, including anticancer, anticonvulsant, antidiabetic, antiviral, antituberculosis, among many others.[27] Drugs with the aminothiazole motif that are currently in the market include Famotidine, Cefdinir, Meloxcam, Abafungin, Meloxicam, and Sudoxicam.[28] In addition, aminothiazoles and its derivatives have also found use as dyes, films and in biophysical binding assays.[29] Herein, we report a leaving group-free synthetic protocol to access aminothiazoles using tetraiodofluorescein as a photocatalyst, under irradiation with green LED at ambient conditions.

The optimization studies were conducted by reacting 1 mmol each of methyl acetoacetate **1a** and thiourea **2a** using 2 mol % of the photocatalyst in acetonitrile as the solvent in a system open to air. Irradiation was by green LED strips (λ = 525 nm) for 8 h (Table 1). With the disodium salt of fluorescein dye, Na_2-eosin Y, as photocatalyst, the yield of the aminothiazole product **3a** was only 10 % (Table 1, entry 1). Other disodium salt derivatives of fluorescein including erythrosin B, phloxine B and Rose Bengal also exhibited low yields of **3a** (Table 1, entries 2-4). On the other hand, reactions using the free acid fluorescein derivatives, eosin Y and tetraiodofluorescein, as photocatalyst proceeded with product yields of 83 % and 98 %, respectively (Table 1, entries 5 and 6). No product **3a** was formed in the absence of a photocatalyst (Table 1, entry 7). **3a** was also not formed when the reaction was conducted in the dark in the presence of tetraiodofluorescein (Table 1, entry 8). These results confirm that the reaction is photocatalytic in nature. Besides studying the effects of different photocatalysts, various solvents were also screened for the reaction with tetraiodofluorescein as photocatalyst but none were as good as MeCN (Table 1, entries 9-11). The

Table 1. Optimization parameters.[a]



Entry	Photocatalyst	Solvent	Yield **3a** (%)[b]
1	Na_2-eosin Y	MeCN	10
2	Erythrosin B	MeCN	17
3	Phloxine B	MeCN	10
4	Rose Bengal	MeCN	12
5	Eosin Y	MeCN	83
6	Tetraiodofluorescein	MeCN	98
7	—	MeCN	0
8[c]	Tetraiodofluorescein	MeCN	0
9	Tetraiodofluorescein	DMF	69
10	Tetraiodofluorescein	EtOH	93
11	Tetraiodofluorescein	DCE	43
12[d]	Tetraiodofluorescein	MeCN	0

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol) and photocatalyst (2 mol %), solvent (6 mL), 8 h, rt in open air and under irradiation of 5050 SMD green LED strips (λ = 525 nm). [b]Isolated yield. [c]Reaction performed in the dark. [d]Under argon.

product **3a** was not observed when the reaction was conducted under argon, implying that the presence of O_2 (air) is essential for the reaction (Table 1, entry 12).To the best of our knowledge, the employment of tetraiodofluorescein in a photochemical reaction has not been reported before.

Using the optimized conditions, a variety of 1,3-dicarbonyls were screened for their suitability in the reaction (Table 2). Various linear and branched alkyl acetoacetates including isopropyl, *tert*-butyl, amyl, and isoamyl reacted smoothly with thiourea **2a** giving excellent yields of **3a**-**3e**. It was gratifying to see that both allyl and methoxyethyl acetoacetate were suitable for the reaction with excellent yields as well (Table 2, **3f** and **3g**). *β*-ketoesters containing *n*-propyl and isopropyl moieties were also well tolerated under the optimized conditions with good yields of products **3h** and **3i**. Both aliphatic and cyclic diketones proceeded smoothly to afford good yields of **3j** and **3k**. *β*-Ketoamide was also a suitable coupling partner with thiourea, forming 83 % of **3l**.

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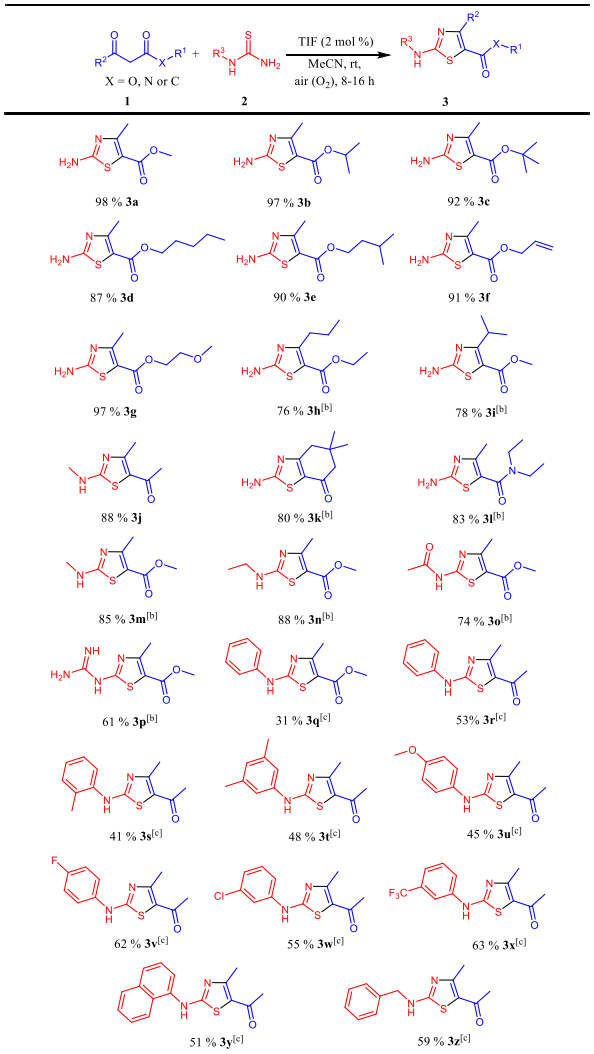
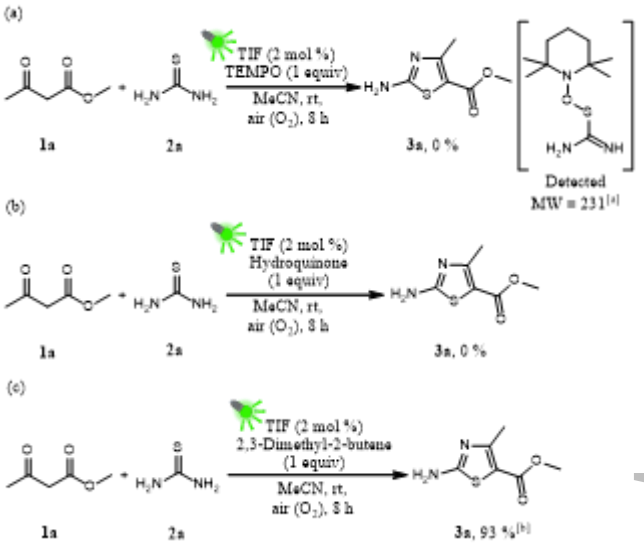
Table 2. Scope of reaction.[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol) and tetraiodofluorescein (2 mol %), MeCN (6 mL), 8 h, rt in open air and under irradiation of 5050 SMD green LED strips (λ = 525 nm). Isolated yield. [b]After 10 h. [c]1.5 mmol of 1,3-dicarbonyl and 16 h instead.

A wide array of *N*-substituted thioureas was also screened for the reaction. *N*-methyl and *N*-ethylthioureas reacted smoothly with methyl acetoacetate **1a** with good yields, albeit with longer reaction times (Table 2, **3m** and **3n**). Reaction of **1a** with *N*-acetyl and guanidyl thiourea derivatives gave moderate yields of **3o** and **3p** respectively. On the other hand, *N*-phenylthiourea fared poorly with 31 % yield of **3q**, even with excess of methyl acetoacetate **1a**. This was due to the competing decomposition reaction of *N*-phenylthiourea into ammonia and phenyliso-thiocyanate, which were detected by GC-MS. It was gratifying to see that acetylacetone fared significantly better, with 53 % yield of **3r** when reacted with *N*-phenylthiourea. Acetylacetone is a more reactive coupling partner than methyl acetoacetate **1a**, presumably because it forms the enol more readily compared to **1a**. This suggests that the



[a] Molecular weight determined by GC-MS. [b] Isolated yield

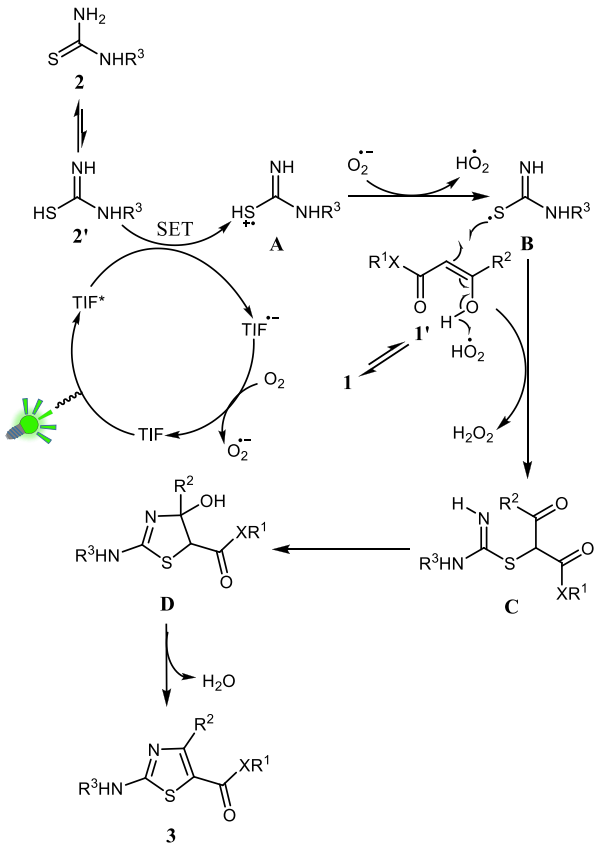
Scheme 2. Control experiments

enol tautomer plays an important part in this reaction. In general, *N*-arylthioureas bearing electron donating substituents on the phenyl ring, including methyl and methoxy (Table 2, **3s - 3u**), fared significantly poorer than those bearing electron donating substituents and halogens (Table 2, **3v - 3x**). *N*-substituted naphthyl and benzyl derivatives were also screened as coupling partners to acetylacetone and formed moderate yields of **3y** and **3z** respectively.

To obtain insights into the reaction mechanism, a series of control experiments were conducted (Scheme 2). First, 1 equiv of 2,2,6,6-tetramethylpiperidin-1-yl oxyl (TEMPO) was added as a radical scavenger to a reaction mixture under optimized conditions (Scheme 2a). After 8 h, no **3a** was detected, indicating that radical intermediates are involved in its formation. An addition product between TEMPO and the thio radical form of **2a** could be identified by GCMS (Scheme 2a), providing evidence of a radical intermediate. Another radical quenching experiment was conducted under the optimized conditions but with a different radical scavenger, hydroquinone (Scheme 2a). Again, no **3a** was detected, supporting the hypothesis that the reaction proceeds via a radical pathway. As it was demonstrated that O_2 was necessary for the reaction (Table 1, entry 12), a singlet O_2 scavenger, 2,3 dimethyl-2-butene, was added to the reaction mixture (Scheme 2c).[30] The reaction was not quenched, suggesting that singlet O_2 does not participate in the reaction but rather the involvement of triplet O_2 is indicated. An experiment was also conducted using the optimized conditions with light alternately switched on/off to prove that a continuous light irradiation is necessary.[31] The concentration of **3a** grew during each irradiation period, but remained unchanged when the light was switched off. This demonstrated that the formation of the desired

product occurred only under continuous light irradiation.

Based on the results obtained from optimization, scope of reaction and control experiments, a plausible mechanism is proposed (Scheme 3). Upon visible light irradiation, the photoredox catalyst tetraiodofluorescein (TIF) goes to its excited state (TIF*).[32] Single electron transfer (SET) from the thiol tautomer of thiourea to TIF* and generates a TIF radical anion ($TIF^{\bullet-}$) and a radical cation **A**.[15] Aerobic oxygen then oxidizes $TIF^{\bullet-}$ back to the ground state, completing the reductive quenching cycle and generating a superoxide radical anion $O_2^{\bullet-}$ in the process.[33] This radical anion then abstracts a hydrogen atom from **A**, forming the thiol radical intermediate **B**. Next, **B** undergoes a radical addition reaction with the enol tautomer of **2**, generating **C** and releasing H_2O_2 in the process.[34] The presence of H_2O_2 was detected with potassium iodide/starch paper, which turned dark blue when a drop from the concentrated reaction mixture was applied on it.[30] Cycloisomerization of **C** then forms **D**, which undergoes dehydration to form the desired product **3**



Scheme 3. Proposed mechanism

In summary, we have developed a novel leaving group-free protocol for the radical coupling of 1,3-dicarbonyls and thioureas to access a wide array of aminothiazoles. The use of photon energy replaces the need for a leaving group and thermal energy, constituting a green and atom economical synthesis. Tetraiodofluorescein was employed as a photoredox catalyst to generate a thio radical *in situ* from thiourea. This then adds to the enol tautomer, forming the aminothiazole backbone in a series of cascade steps.

Experimental Section

Typical procedure for the synthesis of aminothiazoles

A test tube was charged with methyl acetoacetate **1a** (108 µL, 1.0 mmol), thiourea **2a** (76 mg, 1.0 mmol) and tetraiodofluorescein E (17 mg, 0.02 mmol) in 6 mL of MeCN. The test tube was placed in a 8-port holder of the photoreactor (Figure S1, supplementary information). The reaction mixture was stirred in open air under irradiation from 5050 SMD green LED strips [60.0 W at 0.2 W/LED chip, λ = 525 nm] at room temperature. After 8 h, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4. After filtration, the solvents were removed by rotary evaporation and the residue was purified by column chromatography (ethyl acetate/hexane, 3:2 v/v) to afford **3a** in 98 % yield.

Methyl 2-amino-4-methylthiazole-5-carboxylate (3a). Obtained as a white solid (168 mg, 98 %); ^{1}H NMR (300 MHz, DMSO-d6) δ 7.71 (s, 2H), 3.67 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.3, 162.3, 159.6, 106.9, 51.2, 17.1. HRMS (ESI) calcd for $C_6H_7N_2O_2S$ $[M-H]^-$ 171.0234; found 171.0231.

Acknowledgements

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[31] See supporting information (Fig. S2, page S40) for more information regarding the On-Off experiment.

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Visible Light-Mediated Coupling of Thioureas with 1,3-Dicarbonyls: Towards a Leaving Group-Free Synthesis of Aminothiazoles

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