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A Mild Photocatalytic Synthesis of Guanidine from Thiourea under Visible Light

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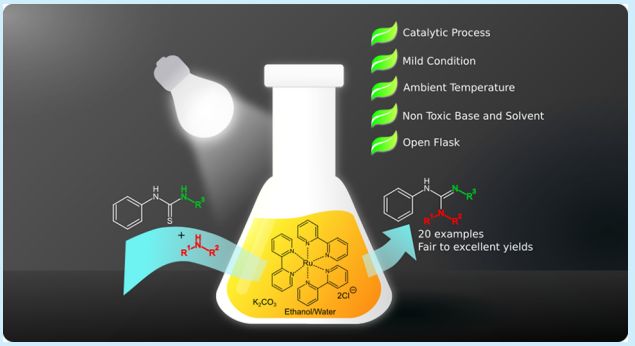
ABSTRACT: In this work, we developed the catalytic guanylation of thiourea using $Ru(bpy)_3Cl_2$ as a photocatalyst under irradiation by visible light. The conversion of various thioureas to the corresponding guanidines was achieved using 1−5 mol % of photocatalyst in a mixture of water and ethanol at room temperature. Key benefits of this reaction include the use of photoredox catalyst, low-toxicity solvents/base, ambient temperature, and an open-flask environment.



Guanidine has been known as an important class of *N*-containing compounds, which are important building blocks for pharmaceutical and chemical industry, due to their broad spectrum of bioactivities.[1−6] Examples of important commercialized compounds containing guanidine groups such as Pinacidil used as a treatment drug for hypertension[7] and NC-174, a high potency synthetic sweetener,[8] are shown in Figure 1.

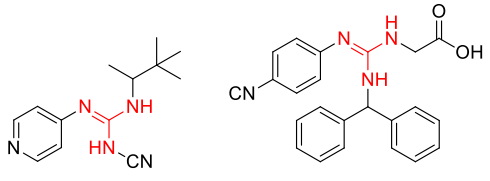
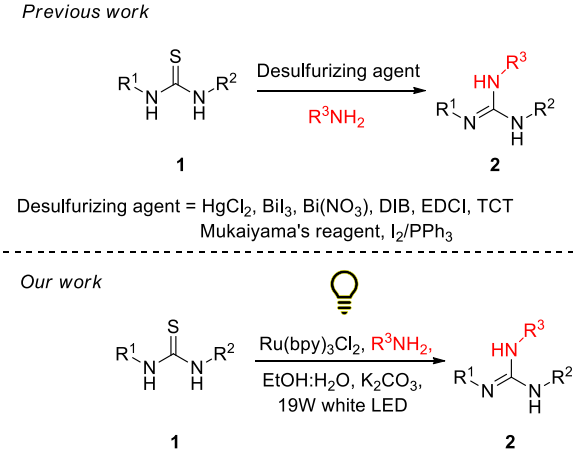


Figure 1. Important guanidine derivatives.

Typically, guanidine is prepared from amines using various guanylating agents[9−11] such as isothioureas,[12] cyanamide,[13] amidine,[9] carbodiimide,[14] triflylguanidines,[15] pyrazole-1-carbox imidamides,[16] and thiourea.[17] However, the use of some guanylating agents suffers from either multiple step synthesis of starting materials or stoichiometric use of oxidants. Among guanylating agents, thioureas are the most promising because of their stability and ease of preparation.[18−20] The conversion of thiourea into guanidine involves the treatment of amine with various desulfurizing agents (Scheme 1). For example, mercury chloride,[21] copper chloride,[17] and Bi(III)/BiO_3[22] have been extensively used. Even though such reagents are highly efficient and compatible with wide variety of functional groups, they require the use of stoichiometric toxic metals. On the other hand, for nonmetal reagents, Burgess's reagent,[23] Mukaiyama's reagent,[24] TCT (trichloro cyanuric acid)[25] and I_2/PPh_3,[26] and hypervalent iodine[27,28] were reported as guanylating agents. Although these reagents produced high yields of guanidines, the reaction usually required harsh reaction conditions,

Scheme 1. Synthetic Approaches for The Preparation of Guanidines



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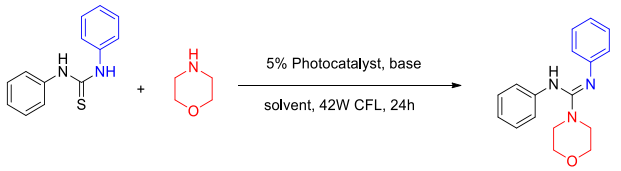
complex operating procedures, and stoichiometric amounts of oxidants. Regarding the concept of green chemistry where catalytic processes that improve the atom economy and reduce waste are preferred, a catalytic preparation of guanidine would be highly attractive for both academic and industrial adoption.

In recent years, photochemical reactions mediated by visible light have drawn significant attention in the organic synthesis community.[29−39] The process allows utilization of low energy and highly abundant visible light in the solar spectrum to perform chemical reactions via the utilization of photocatalyst creating a new paradigm of environmentally friendly processes in organic transformation. Among them,[29] photocatalytic oxidation of various organosulfur compounds under visible light has been established[40−57] and, more recently, visible-light-induced desulfurization of organosulfur followed by amination has been applied in C−N bond construction. Tan and co-workers demonstrated a visible-light-promoted amide formation from the reaction between amines and potassium salts of thioacids.[53] Recently, our group also reported direct amination of 2-mecaptobenzoxazole with amines using Rose Bengal as a photocatalyst to prepare the corresponding aminobenzoxazoles.[58] As part of our continuing studies on the oxidation of organosulfur,[27,58−61] we plan to apply the concept of photomediated desulfurization to guanidine synthesis. Herein, we reported a new visible light promoted process to prepare guanidines from thioureas and amines. To the best of our knowledge, this is the first catalytic process for guanylation of thiourea

For the optimization study, we used diphenyl thiourea (**1a**) and morpholine as a model substrate for guanylation reaction as shown in Table 1. Initially, the reaction was carried out in the presence of 5% mol of catalysts under the household 42 W CFL at room temperature under an open-air atmosphere (Figure S2). Using an organic dye such as Eosin Y, Rose Bengal, and Safranin O, guanidine **2a** were isolated in 3−72% yield (Table 1, entries 1−5) after 24 h irradiation. By switching the organic dyes to a transition-metal photoredox catalyst, $Ru(bpy)_3Cl_2$, the reaction was improved and **2a** was isolated in 81% yield (Table 1, entry 7). With this result, we then selected $Ru(bpy)_3Cl_2$ as a photocatalyst for further study. Importantly, we also ran a control experiment in parallel. All conditions were replicated except the reaction tube was covered with aluminum foil. Only, ca. 10% of **2a** was observed, suggesting the reaction is mediated by the visible light (Table 1, entry 6). With the promising results in hand, base, solvent, light sources, and the amount of $Ru(bpy)_3Cl_2$ were optimized. Among the bases tested, K_2CO_3, DBU, and $CsCO_3$ gave **2a** in excellent yields (Table 1, entries 7−9) while significantly lower yields were obtained in the case of TEA and DIPEA (Table 1, entries 10 and 11). Considering the toxicity and cost, we decided to use K_2CO_3 as our choice of base for the photoreaction. When the light source was replaced with a 19 W LED which consumes less energy and produces less heat, the reaction still maintained its effectiveness (Table 1, entry 12). Bearing the concept of green chemistry in mind, we replaced acetonitrile with a mixture of ethanol and water due to their low toxicity.[62] To our surprise, the reaction occurred smoothly in a homogeneous fashion and **2a** was obtained in good yield (Table 1, entry 13). Importantly, under 19 W LED irradiation in a mixture of ethanol and water as a solvent, visible-light-mediated guanylation could proceed even with only 1% of catalyst loading to provide the product **2a** in excellent yield (Table 1, entry 14). Moreover, in the absence of catalyst, the reaction did not proceed (Table 1, entry 15) and only starting material **1a** was detected suggesting that the photoredox catalyst is essential for guanylation reaction. Finally, when this photoreaction was conducted under a nitrogen atmosphere, the product **2a** was isolated in 22% yield (Table 1, entry 16). This low yield indicated that oxygen plays an essential role in this reaction. However, the product yield did not drop to zero with several rigorous attempts that may be due to the trace amount of oxygen which still cannot be completely removed or there might be a minor alternative pathway removing the sulfur atom without involvement of oxygen gas.

Table 1. Optimization Studies on Guanylation Reaction[a]



1a **2a**

entry	photocatalyst	solvent	base	yield[b] (%)
1	pyrene	MeCN	K_2CO_3	3
2	Phenazine	MeCN	K_2CO_3	50
3	Eosin Y	MeCN	K_2CO_3	50
4	Rose Bengal	MeCN	K_2CO_3	62
5	Safranin O	MeCN	K_2CO_3	72
6[c]	$Ru(bpy)_3Cl_2$	MeCN	K_2CO_3	10
7	$Ru(bpy)_3Cl_2$	MeCN	K_2CO_3	81
8	$Ru(bpy)_3Cl_2$	MeCN	DBU	80
9	$Ru(bpy)_3Cl_2$	MeCN	Cs_2CO_3	83
10	$Ru(bpy)_3Cl_2$	MeCN	TEA	26
11	$Ru(bpy)_3Cl_2$	MeCN	DIPEA	18
12[d]	$Ru(bpy)_3Cl_2$	MeCN	K_2CO_3	90
13[d]	$Ru(bpy)_3Cl_2$	EtOH/H_2O	K_2CO_3	90
14[e]	$Ru(bpy)_3Cl_2$	EtOH/H_2O	K_2CO_3	91
15[f]	–	EtOH/H_2O	K_2CO_3	–
16[g]	$Ru(bpy)_3Cl_2$	EtOH/H_2O	K_2CO_3	22

[a]Reaction conditions: **1a** (0.5 mmol), morpholine (2.0 mmol), catalysts (0.025 mmol), bases (1.0 mmol), solvents (5.0 mL). [b]Isolated yield. [c]Reaction tube was covered with aluminum foil. [d]19 W white LED as light source. [e]19 W white LED as light source and 0.005 mmol of catalyst. [f]Room light. [g]The reaction was conducted under a N_2 atmosphere.

To expand the scope of reaction, various amines were tested in the guanylation reaction with diphenyl thiourea (**1a**) under the optimized conditions (Scheme 2). Primary amines such as butylamine, benzylamine, cyclohexylamine, and *β*-Alanine ethyl ester reacted smoothly under the optimized conditions providing the corresponding guanidine **2b−2e** respectively, in excellent yields. For ethanolamine, which contains both O and N nucleophilic atoms, the C−N bond formation occurred selectively, giving product **2f** in 80% yield. Then, we expanded the amine substrate into secondary amines. When diethylamine was used as a nucleophile, product **2g** was obtained in 82% yield after an extended reaction time of 3 days. Next, a variety of cyclic amines such as 2-methylpiperidine, pyrrolidine, azepine, and BOC-protected piperazine were tested and products **2h−2k** were isolated in moderate to high yields. Unfortunately, a less nucleophilic amine such as aniline failed to give the expected **2l** and only the starting thiourea **1a** was observed.

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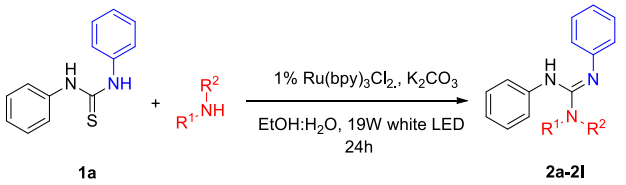
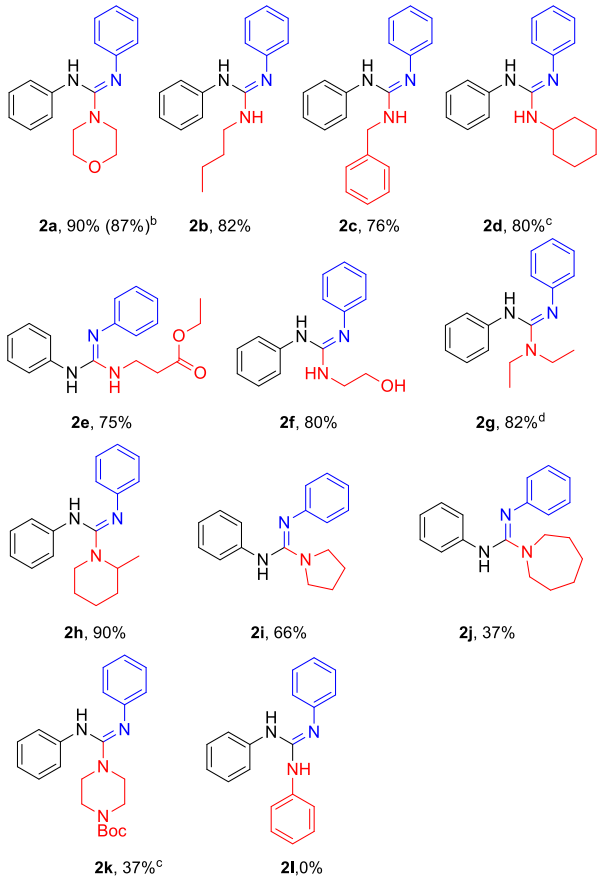
Scheme 2. Substrate Scope of Amine with 1,3-Diphenylthioureaa[a]

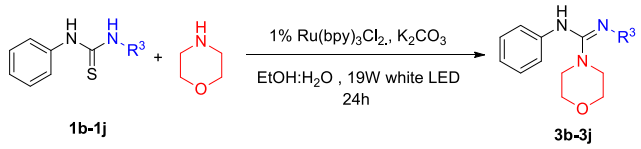


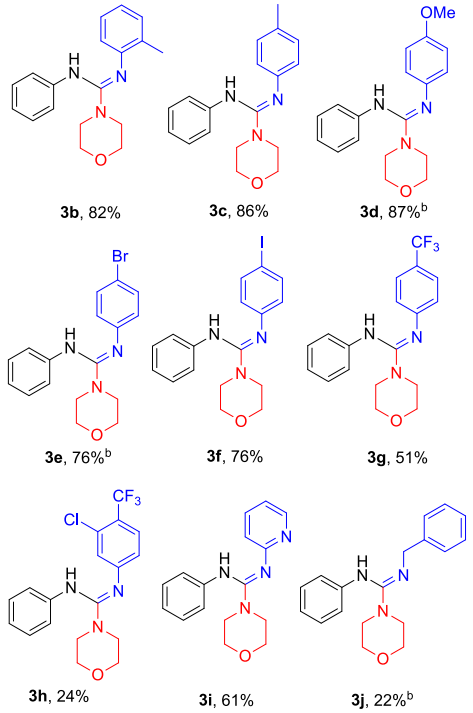


[a]Reaction conditions: **1a** (0.5 mmol), amines (2.0 mmol), Ru(bpy)$_3$Cl$_2$ (0.005 mmol), K_2CO_3 (1.0 mmol), in EtOH/H_2O (9:1) 5.0 mL, isolated yields. [b]Reaction was conducted using **1a** in 1 mmol. [c]Ru(bpy)$_3$Cl$_2$ (0.025 mmol). [d]Reaction was carried out for 3 days.

With successful guanylation of **1a**, we extended the scope of this reaction further to other thiourea substrates (Scheme 3). Diphenyl thiourea containing an electron-donating group such as methyl (**1b**−**1c**) and methoxy (**1d**) reacted with morpholine to provide guanidines **3b**−**3d** in excellent yields. Moreover, for halide-substituted thiourea with halides such as the bromo (**1e**) and iodo group (**1f**), the expected products **3e** and **3f** were isolated in high yields. Thiourea carrying an electron-deficient group such as a trifluoromethyl (**1g**) and chloride/trifluoromethyl (**1h**) group had an effect on the reaction, as low to moderate yields of target guanidines (**3g**−**3h**) were obtained. This group may decrease electron density that suppresses the oxidation of thiourea which will be further discussed in the mechanistic investigation. *N*-Heterocycle thioureas such as pyridine (**1i**) were also found to be compatible with the optimized conditions delivering the

Scheme 3. Substrate Scope of Thiourea with Morpholine[a]





[a]Reaction conditions: **1b**−**1j** (0.5 mmol), morpholine (2.0 mmol) Ru(bpy)$_3$Cl$_2$ (0.005 mmol), K_2CO_3 (1.0 mmol), in EtOH/H_2O (9:1) 5.0 mL, isolated yields. [b]Ru(bpy)$_3$Cl$_2$ (0.025 mmol)

product **3i** in 61% yield. Unfortunately, the benzyl thiourea **1j** only provided the desired product **3j** in 22% yield. This may be caused by the low stability of the benzyl group in **1j** under the radical reaction, as there was no starting thiourea left in the reaction. For other alkyl thioureas, the reaction was sluggish and the starting thioureas were mostly recovered. Currently, this new photoreaction is thus effective for the synthesis of guanidines from aryl substituted thioureas but not from the alkyl thioureas. Therefore, the photocatalytic conversion of alkyl thioureas to the corresponding guanidines remains very challenging.

To simplify the synthetic method, we combined the photoguanylation step with the thiourea formation step. Isocyanate (**4**), *para*-toluidine, and morpholine were mixed with a ruthenium catalyst and irradiated under white LED for 24 h (Scheme 4). The reaction exclusively provided guanidine product **3c** in 68% yield. The process allows construction of structurally diverse guanidines directly from commercially available isothiocyanate in a one-pot fashion, and the process may also be considered as multicomponent reactions (MCRs).

To propose a plausible reaction mechanism of this new visible-light photoredox-catalyzed guanylation reaction, several mechanistic studies were conducted. We irradiated **1a** under a 19 W white LED light bulb for 24 h under optimized conditions without the addition of amine. Although complex mixtures were produced in the crude product, the

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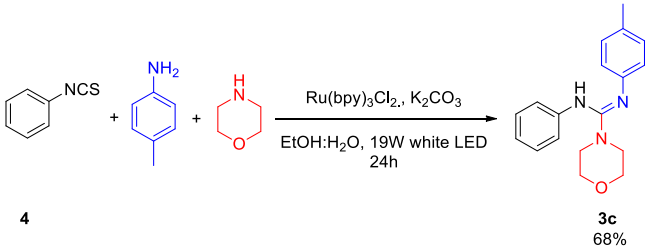
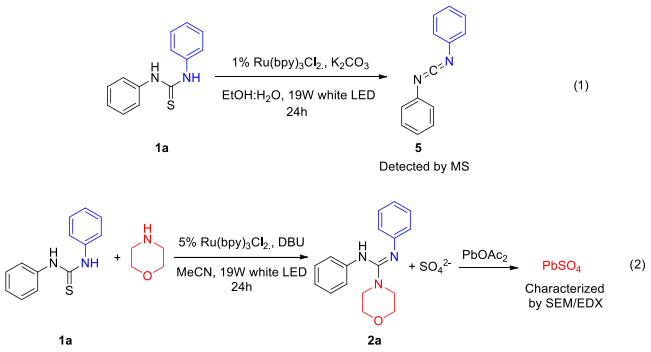
Scheme 4. One-Pot Synthesis of Guanidine from Isothiocyanate[a]



[a]Reaction conditions: **4** (0.5 mmol), *p*-toluidine (0.75 mmol), morpholine (2.0 mmol), $Ru(bpy)_3Cl_2$ (0.005 mmol), K_2CO_3(1.0 mmol), in EtOH/H_2O (9:1) 5.0 mL. Isolated yields.

carbodiimide **5** (Scheme 5 eq 1) intermediate was observed in the mass spectrum of the crude product (Figure S43). This suggested that **5** could serve as a key intermediate in our photoreaction.

Scheme 5. Mechanistic Investigation Experiment

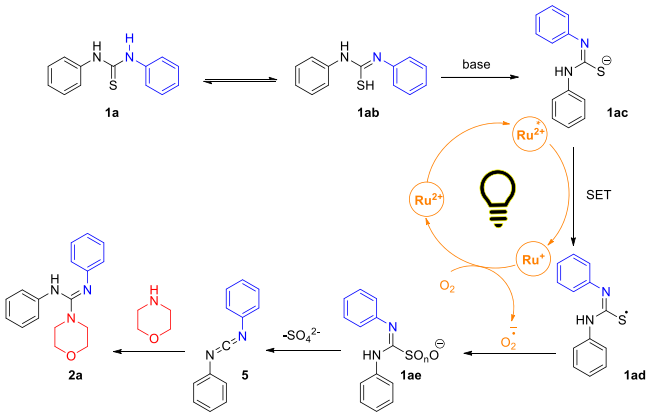


Moreover, we successfully trapped the sulfur-containing byproduct as a precipitate by the addition of $Pb(OAc)_2$ (Scheme 5. eq 2). It is important to note that the trapping experiment was conducted by using DBU as a base and MeCN as a solvent (Table 1, entry 8) to avoid the solid interference from potassium carbonate salt. The yellow precipitate was filtered and characterized with SEM/EDX, revealing that the byproduct was lead sulfate (Figure S63 and Table S1).

Based on the results of the mechanistic studies, we proposed a visible-light-catalyzed guanylation reaction as shown in Scheme 6. First, the reaction starts with tautomerization of **1a** to the **1ab** intermediate. Then, the **1ab** intermediate is deprotonated by a base and transformed into radical intermediate **1ad** via photo-single-electron transfer (SET) to the ruthenium(II) catalyst. Oxidative coupling between radical intermediate **1ad** and superoxide produce a peroxysulfur intermediate **1ae**. Then, sulfate was released to form a carbodiimide as key intermediate **5** which was consequently attacked by the morpholine at the carbon atom to produce guanidine product **2a**.[63] In this proposed mechanism, the oxygen molecule serves as the terminal oxidant and catalyst regenerator that allows the reaction to proceed without additional oxidants.

In summary, a mild photocatalytic guanylation of thiourea has been developed for the synthesis of guanidines. The reaction showed good compatibility with several reactive functional groups such as alcohol, halides, and ester. The mechanistic study suggested a photooxidation of thiourea by

Scheme 6. Proposed Mechanism



ruthenium(II) via a single-electron transfer process followed by reaction with an oxygen species to generate a peroxysulfur intermediate which rapidly desulfurizes to a carbodiimide intermediate. The reaction is relatively green and convenient to conduct, as it can be performed in safe solvent (ethanol/water) at ambient temperature in an open flask without additional oxidant. This reaction should provide an environmentally friendly synthetic route to various guanidines useful for medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02770.

General procedure, materials and methods, copies of ^1H and ^{13}C NMR and HRMS spectra of compounds **2a**−**3j**, and EDX-SEM spectrum of $PbSO_4$ (PDF)

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Notes

The authors declare no competing financial interest.

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