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Visible-light-induced *N*-alkylation of anilines with 4-hydroxybutan-2-one†

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The synthesis of amines through *N*-alkylation is particularly attractive. Herein, a strategy for visible-light-induced *N*-alkylation of anilines with 4-hydroxybutan-2-one was developed in the presence of NH₄Br, which avoid the use of metals, bases and ligands. In addition, gram-scale experiments proved that the system has the potential to be scaled.

Introduction

Nitrogen-containing compounds are valuable reactive intermediates and widely present in pharmacologically relevant therapeutic agents, natural products, and agricultural chemicals. For instance, fluoxetine,¹ which is a type of medication known as a selective serotonin reuptake inhibitor (SSRI), is the primary component in various psychotropic drugs used to treat conditions such as depression, obsessive-compulsive disorder, anxiety disorder, and bulimia nervosa. Clobenzorex,² an amphetamine appetite suppressant, is indicated for a variety of obesity diseases. Cinacalcet³ has been investigated as a CYP2D6 inhibitor for the treatment of secondary hyperparathyroidism in dialysis patients (Fig. 1).

N-Alkylation is an essential method for synthesizing nitrogen-containing compounds, especially *N*-alkylation of amines with alcohols, which has advantages of easily accessible raw materials, the sole by-product (H₂O) and high atom economy. The research on *N*-alkylation is mostly focused on thermal catalysis. For instance, in the pioneering work by Grigg⁴ and Watanabe,⁵ transition metal catalysts were used for the *N*-alkylation of amines at high temperature (>100 °C). Subsequently, researchers have successively developed various catalytic systems, among which transition metals play an important role, for instance, transition metals Ir,⁶ Ru,⁷ Au,⁸ Pd,⁹ Fe,¹⁰ Ni,¹¹ and Cu¹² are widely used due to their good catalytic properties (Scheme 1). However, the metal residue limits their application in pharmaceutical intermediates. In addition, additional strong bases and harsh conditions with high temperature are also limitations that need to be faced.

Due to light is a renewable and clean energy source, especially in recent years, photocatalysis has attracted widespread attention from researchers. Meanwhile, photocatalytic *N*-alkylation of alcohols and amines has also been reported, such as Cu–Mo/TiO₂,¹³ Au/TiO₂,¹⁴ eosin Y,¹⁵ ZnIn₂S₄ nanosheets,¹⁶ and copper/bisphosphine/phenoxide complex¹⁷ *et al.* (Scheme 1). In the past few years, we have been devoting our efforts towards the synthesis and applications on *N*-alkylation with alkali-free and transition metal-free catalysis and achieved interesting results.¹⁸ Herein, we present a strategy for visible-light-induced C–N coupling in nitrogen atmosphere, which is a novel method

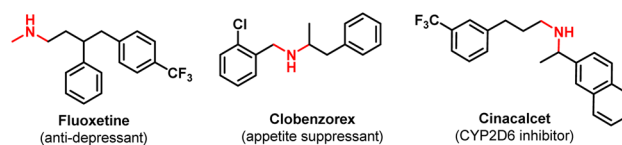
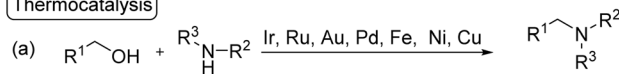


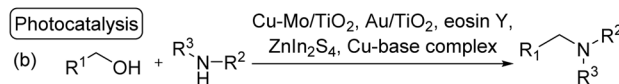
Fig. 1 Representative examples of pharmaceutically important nitrogen-containing compounds moieties.

Previous work:

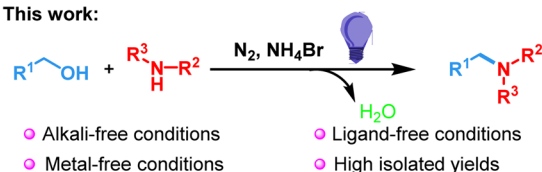
Thermocatalysis



Photocatalysis



(c) This work:



Scheme 1 *N*-Alkylation of amines with alcohols.

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for synthesizing β -amino ketone in the absence of additional base with the advantages of environmentally friendly and mild reaction conditions.

Experimental section

General considerations

All the reagents including aromatic amines, 4-hydroxybutan-2-one, ammonium bromide, anilines, solvents were purchased from commercial sources and were used without further purification. All chemical shift values refer to δ TMS = 0.00 ppm or CDCl₃ (δ (¹H), 7.26 ppm; δ (¹³C), 77.2 ppm). All the melting points were uncorrected. Analytical TLC plates were viewed by UV light (254 nm). Column chromatographic purifications were performed on SDZF silica gel 160.

General experimental procedure

A 15 mL RBF was subsequently charged with 0.5 mmol aromatic amines, 0.525 mmol 4-hydroxybutan-2-one, 20 mol% NH₄Br (9.8 mg), 2 mL hexane, and then a nitrogen balloon was equipped to replace the air inside the RBF with a vacuum pump. The resulting mixture was performed under a 50 W 420 nm LED at 25 °C for 12 h. After reaction was complete, the solvent was removed by vacuum distillation and resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1 : 20–1 : 4) to afford the desired products.

Experimental procedure on gram scale

A 50 mL RBF was subsequently charged with 10 mmol aromatic amines, 10.5 mmol 4-hydroxybutan-2-one, 20 mol% NH₄Br, 20 mL hexane, and then a nitrogen balloon was equipped to replace the air inside the RBF with a vacuum pump. The resulting mixture was performed under a 50 W 420 nm LED at 25 °C for 48 h. After reaction was complete, the solvent was removed by vacuum distillation and resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1 : 20–1 : 4) to afford the desired products.

Results and discussion

Initially, aniline (**1a**) and 4-hydroxybutan-2-one (**2a**) were selected as the model substrates to optimize the reaction conditions (Table 1). To our delight, when the mixture of **1a** and **2a** in THF solvent was exposed to 50 W 420 nm LED irradiation at room temperature for 12 h, 4-(phenylamino)butan-2-one (**3a**) was obtained in 18% isolated yield (entry 1). Moreover, a brief screening of other solvent systems such as MeCN, H₂O, MeOH, dimethyl sulfoxide (DMSO), hexane and solvent-free system yielded 4-(phenylamino)butan-2-one (**3a**) in 5–77% isolated yields (Table 1, entries 2–7), and hexane proved to be more suitable for the reaction in 77% isolated yield (Table 1, entry 6). Comparing light sources between 20, 50, and 100 W LEDs showed that decreasing and increasing the power decreased the yield of the reaction from 77% to 59% and 60%, respectively (entries 8–9). Various additives were tested, such as NH₄Cl, NH₄F, (NH₄)₂SO₄, and NH₄Br, and NH₄Br was found to be the

Table 1 Optimization of reaction conditions

Entry	LED	Additive (mol%)	Solvent	Yield ^a (%)
1	50 W 420 nm	—	THF	18
2	50 W 420 nm	—	MeCN	5
3	50 W 420 nm	—	H ₂ O	43
4	50 W 420 nm	—	MeOH	38
5	50 W 420 nm	—	DMSO	45
6	50 W 420 nm	—	Hexane	77
7	50 W 420 nm	—	—	59
8	20 W 420 nm	—	Hexane	59
9	100 W 420 nm	—	Hexane	60
10	50 W 420 nm	NH ₄ Cl (10)	Hexane	81
11	50 W 420 nm	NH ₄ F (10)	Hexane	32
12	50 W 420 nm	(NH ₄) ₂ SO ₄ (10)	Hexane	59
13	50 W 420 nm	NH ₄ Br (10)	Hexane	86
14	50 W 420 nm	NH ₄ Br (20)	Hexane	94
15	50 W 420 nm	NH ₄ Br (30)	Hexane	83
16	50 W 420 nm	NH ₄ Br (40)	Hexane	62
17 ^b	50 W 420 nm	NH ₄ Br (20)	Hexane	98
18 ^{b,c}	50 W 420 nm	NH ₄ Br (20)	Hexane	87
19 ^{b,d}	50 W 420 nm	NH ₄ Br (20)	Hexane	79
20 ^b	—	NH ₄ Br (20)	Hexane	Trace
21 ^b	50 W 420 nm	—	Hexane	31

^a Isolated yield. ^b Reaction condition: additive (20 mol%), **1a** (0.5 mmol), **1b** (0.525 mmol), hexane (2 mL), and room temperature for 12 h under N₂. ^c Reaction time was 18 h. ^d Reaction time was 9 h.

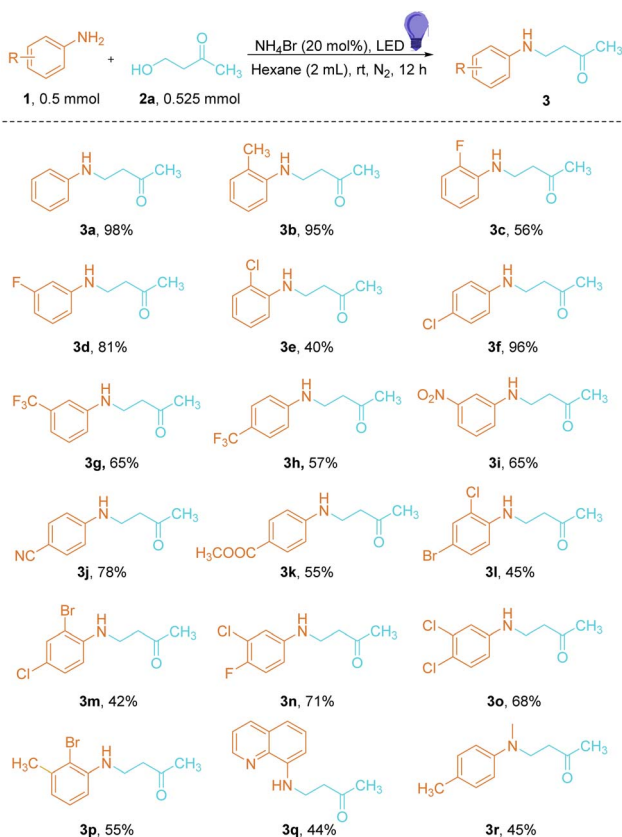
most efficient one to facilitate the desired product formation (entries 10–13). Increasing the amount of NH₄Br from 10 mol% to 20 mol% improved the isolated yield to 94%, whereas further increasing the amount of NH₄Br (30 mol% and 40 mol%) lowered the isolated yields to 83% and 62%. It might be due to the excess additive interfered with mass transfer. The isolated yield of **3a** could be obtained in a 98% isolated yield when the dosage of **2a** was increased to 0.525 mmol (entry 17). These results demonstrate a slightly excess substrate can increase the reaction yield. Subsequently, increasing and reducing reaction time also gave inferior results (entries 18–19). Finally, control experiments were conducted and trace product **3a** and 31% isolated yield of **3a** were observed in the absence of light or NH₄Br, emphasizing the essential role of light and NH₄Br in the catalytic system (entries 20–21). Based on the above results, the optimum conditions for the *N*-alkylation reaction are NH₄Br (20 mol%) as additive and hexane as solvent in a nitrogen atmosphere under 50 W 420 nm LED irradiation at room temperature.

With the optimized conditions in hand, we next explored the scope of aromatic amines with 4-hydroxybutan-2-one (Scheme 2). Overall, various substituted aromatic amine compounds with electron-donating and -withdrawing groups could undergo reactions smoothly with moderate to good yields (40–98%). To our delight, the *ortho*-methyl substituted aromatic amine could also be tolerated, generating the corresponding *N*-

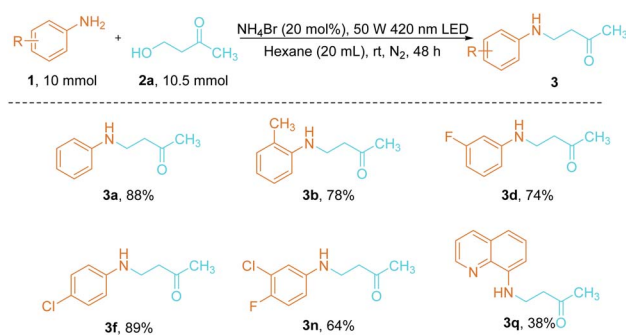
alkylation product **3b** with 95% isolated yields. We next explored two classes of haloarenes, fluoric- and chloro-arylamines (**3c–3f**) with moderate to good isolated yields (40–96%), demonstrating existed significant steric hindrance effect. Furthermore, the different electron-withdrawing, such as *m*-CF₃, *p*-CF₃, *m*-NO₂, *p*-CN and *p*-COOCH₃ were also efficiently converted into the corresponding products (**3g–3k**) in 65%, 57%, 65%, 78% and 55% yields, respectively. In addition, multi substituted anilines can also obtain the target products (**3l–3p**) with medium yields (45%, 42%, 71%, 68% and 55%). Remarkably, 8-aminoquinoline with greater steric hindrance can also react smoothly with 4-hydroxy-2-butanone with 44% yield (**3q**). Finally, changing primary aromatic amines to secondary aromatic amines was compatible with producing the desired product **3r** in 45% yield.

Gram-scale (10 mmol) reactions were conducted using anilines and 4-hydroxybutan-2-one at 48 h to demonstrate the practicality of the current method. The desired products were obtained with satisfactory yields (Scheme 3), manifesting that this protocol serves as a practical approach for synthesizing β -amino ketones.

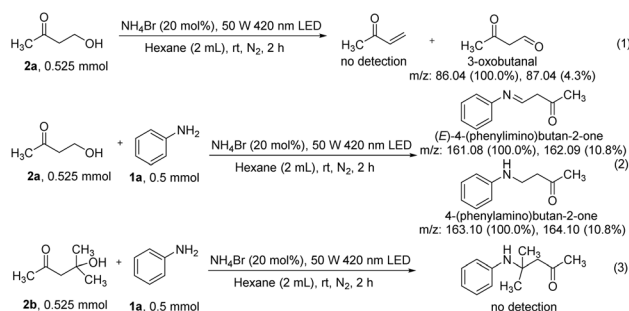
A series of control experiments were performed to demonstrate the possible reaction mechanism through GCMS detection (Scheme 4). Initially, we evaluated the reaction of 4-hydroxybutan-2-one under standard conditions and detected the generation of 3-oxobutanal (Scheme 4, eqn (1)). We speculated that the 3-oxobutanal may be an intermediate experienced



Scheme 2 Scope of substrates (isolated yield).



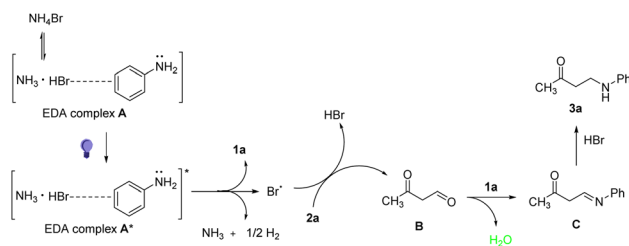
Scheme 3 Gram scale reactions (isolated yield).



Scheme 4 Control experiments.

in the reaction process. Similarly, 4-hydroxybutan-2-one and aniline reacted under standard conditions, and the presence of 4-(phenylimino)butan-2-one and 4-(phenylamino)butan-2-one was detected by GCMS (Scheme 4, eqn (2)), suggesting that 4-(phenylimino)butan-2-one may be an intermediate experienced during the reaction process. To further prove our assumption, we used 4-hydroxy-4-methylpentan-2-one for the reaction and did not find the corresponding target product (Scheme 4, eqn (3)), proving that alcohol dehydrogenation is a process experienced during the reaction. In addition, to verify the existence of the EDA complex, UV-Vis absorption spectra of **1a** and NH₄Br in the reaction system were recorded, as shown in Fig. S1,[†] when **1a** and NH₄Br were added to methanol, a slight redshift of the absorption occurred.

According to our results and previous literature,^{18b,19} we proposed a possible mechanism (Scheme 5). Firstly, ammonium bromide in equilibrium with NH₃ and HBr, subsequently, NH₃·HBr interacted with aniline to generate EDA complex A,



Scheme 5 Possible reaction pathway.

which transfers to its excited state (EDA complex **A**^{*}) under visible-light irradiation. At the same time, 4-hydroxy-2-butanone **2a** underwent dehydrogenation under the action of Br radical to form intermediate **B**. Intermediate **B** was dehydrated by coupling with aniline to obtain imine intermediate **C**. Subsequently, HBr participated as an H donor in the reaction to obtain the target product **3a**.^{18b}

Conclusions

A strategy for visible-light-induced *N*-alkylation of anilines with 4-hydroxybutan-2-one was developed in the presence of NH₄Br. Metallic catalysts, oxidants, bases and ligands were not involved in this *N*-alkylation reaction which made it more eco-friendly. In addition, gram-scale experiments proved that the system has the potential to be scaled.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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