Organophotoredox-Catalyzed Direct *C-H* Functionalization of "Drug Prejudice" at Room Temperature

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Among the all known *N*-heterocycles, imidazo[1,2-a]pyridines are widely found in biologically active natural products and pharmaceuticals. It is also considered as a "drug prejudice" as it shows antipyretic,[1] antiviral,[2] antibacterial,[3] anticancer,[4] antiulcer[5] and anti-inflammatory[6] properties. There are also marketed drugs such as alpidem, zolpidem, olprinone, necopidem, saripidem, and zolimidine containing imidazo[1,2-a]pyridines as the core. This moiety have also shown significant importance in material chemistry due to its capabilities to exhibit excited-state intramolecular proton transfer.[7] Due to all these reasons, functionalization of imidazo[1,2-a]pyridines at different positions by various groups has drawn considerable attention in last few decades.[8]

In last few years, visible light promoted photoredox process has emerged as a prominent tool for carrying out novel chemical transformations at room temperature.[9] Most common photocatalysts employed to carry out such transformations are ruthenium and iridium based complexes. These precious metal catalysts are very expensive and potentially toxic on larger scale.[10] Therefore major efforts have been made in last few years to use organic dyes as alternative to these expensive complexes. Recently, several reports have been published involving visible light promoted C-H functionalization of imidazo[1,2-a]pyridines at room temperature.[11-22] However, cross coupling between a C (sp^3) carbon and C (sp^2) carbon of imidazo[1,2-a]pyridine is still considered as a challenging task. Nature of the functional group or the substituent attached at the C_3 position of the imidazo[1,2-a]pyridine regulates its biological activity. Many well-developed drugs contain methylene group directly attached to imidazo[1,2-a]pyridines (Fig. 1).To the best of our knowledge, there was no such method for the direct coupling between active methylene compounds and imidazo[1,2-a]pyridines. Therefore to check the impact of presence of active methylene carbon at the C_3 position of the imidazo[1,2-a]pyridine, it was decided to carry out this challenging C-C bond formation reaction under mild and sustainable conditions.

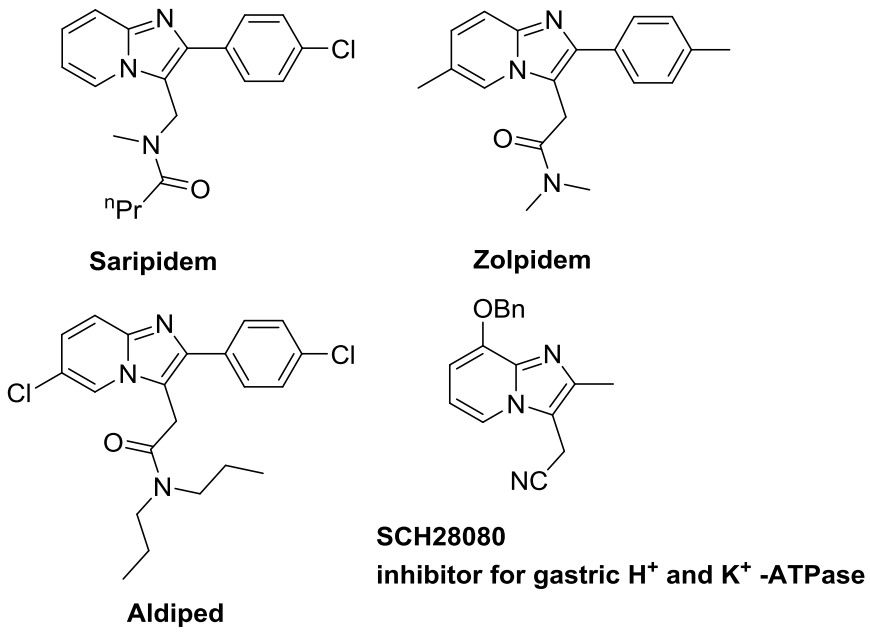
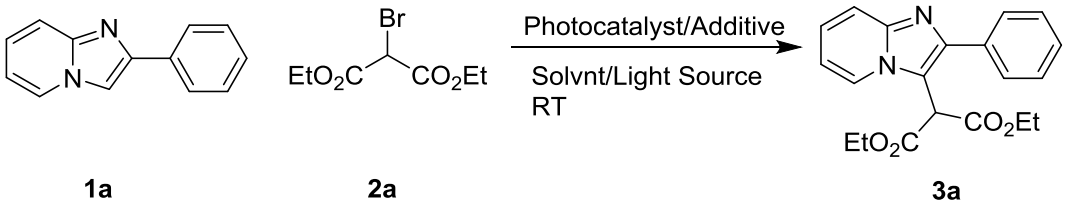


Fig. 1

Results and Discussion:

Table 1: Optimization of Reaction Condition



1a **2a** **3a**

Entry	Photocatalyst (2 mol%)	Light Source (10 W)	Additive	Solvent	Yield (%)
1	EosinY	Blue LED	-	DMSO	**1a** decomposed
2	Eosin Y	Blue LED	B_2Pin_2 (1.5 eq)	DMSO	N.R.
3	Eosin Y	Blue LED	B_2Pin_2 (1.5 eq)	Acetone	N.R.
4	Eosin Y	Blue LED	NHSI (0.2 eq.)/B_2Pin_2 (1.5 eq)	EA	N.R.
5	Eosin Y	Blue LED	NHPI (0.2 eq.)/B_2Pin_2 (1.5 eq)	EA	N.R.
6	Ru	Blue LED	NHPI (0.2	EA	N.R.

	photocatalyst		eq.)/B_2Pin_2 (1.5 eq)		
7	-	Blue LED	TBHP(2 eq.)/Ferrocene (0.2 eq)	EA	NR
8	Rose Bengal	Blue LED	TBHP(2 eq.)	EDC	N.R.
9	Eosin Y	Blue LED	I_2 (1 eq)/K_2CO_3 (1.5 eq)/B_2Pin_2 (1.5 eq)	DMSO	N.R.
10	Ru photocatalyst	Blue LED	I_2 (1 eq)/K_2CO_3 (1.5 eq)/B_2Pin_2 (1.5 eq)	DMSO	N.R.
11	Ru photocatalyst	Blue LED	NBS (1.1 eq.)/NPh_3 (2 eq.)/ B_2Pin_2 (1.5 eq)	DMSO	N.R.
12	Ru photocatalyst	Blue LED	NPh_3 (2 eq.)/ B_2Pin_2 (1.5 eq)	DMSO	20[a]
13	Ru photocatalyst	Blue LED	NPh_3 (2 eq.)/ B_2Pin_2 (1.5 eq)	CH_3CN	32[a]
14	Ru photocatalyst	Blue LED	NPh_3 (2 eq.)/ B_2Pin_2 (1.5 eq)	dioxane	47[a]
15	Rose bengal	Blue LED	NPh_3 (2 eq.)/ B_2Pin_2 (1.5 eq)	dioxane	59[a]
16	**Rose bengal**	**Blue LED**	**$NaHCO_3$ (2 eq.)/ B_2Pin_2 (1.5 eq)**	**dioxane**	**95[a]**
17		Blue LED	$NaHCO_3$ (2 eq.)/ B_2Pin_2 (1.5 eq)	dioxane	Trace[a]
18	Rose bengal		$NaHCO_3$ (2 eq.)/ B_2Pin_2 (1.5 eq)	dioxane	N. R.[a]

[a]Reaction was carried out with bromo diethyl malonate **2a**.

We commenced our study with 2-phenylimidazo[1,2-a]pyridine **1a** (0.5 mmol) and diethyl malonate (1 mmol) in DMSO (5 mL) as reacting partners. When **1a** and diethyl malonate were subjected to 10 W blue LED in the presence of 2 mol% of eosin Y, decomposition of starting material was observed (**Table 1**, entry 1). No reaction observed when 1.5 eq. of bis(pinacolato)diboron (B_2pin_2) was used as an additive but this time **1a** was not decomposed and recovered from reaction mixture (entry 2). Similar observation was reported when this reaction was carried out in acetone (entry 3). Use of *N*-hydroxysuccinimide (NHSI) or *N*-hydroxyphthalimide (NHPI) as the HAT catalyst along with eosin Y/B_2pin_2 system could not produce the required product (entry 4 & 5). Similar result was observed with Ru photocatalyst

(entry 6). Ferrocene/TBHP & rose bengal/TBHP system were also attempted to get the required result (entry 7 & 8 respectively). Later, it was decided to carry out the reaction by in-situ conversion of diethyl malonate to its iodo derivative and the reaction was carried out in the presence of I_2/K_2CO_3 along with B_2Pin_2. This effort also could not produce any fruitful result (entry 9). Replacing eosin Y with Ru photocatalyst could not yield desired result (entry 10). After these unsuccessful efforts, it was decided to use bromodiethyl malonate **2a** (0.5 mmol) instead of diethyl malonate as the coupling partner. When **1a** and **2a** were subjected to $Ru/NPh_3/B_2Pin_2$ system in the presence of 10 W blue LED, a poor yield of the desired coupling product was observed (entry 12). Yield of the reaction was improved to 47% in dioxane (entry 14). The yield was further improved to 59% when rose bengal was used as the photocatalyst (entry 15). We were surprise to observe an excellent yield of 95% by using sodium bicarbonate as the base (entry 16). Hence, in this manner we were successful in develop suitable condition for coupling an active methylene carbon with 2-phenylimidazo[1,2-a]pyridine. Now our next aim was to study the scope of the reaction and getting more functionalized molecules.

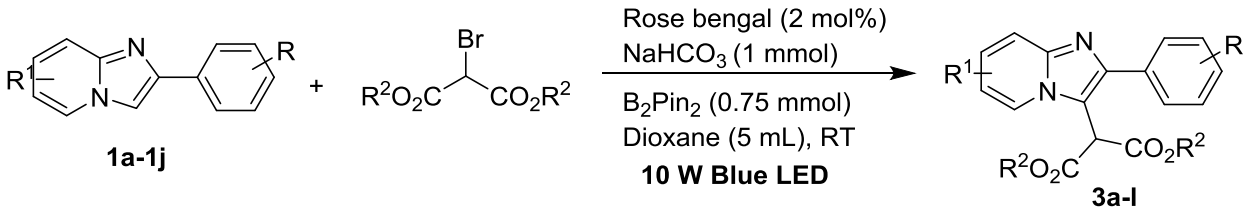
Scope of the Reaction:

After achieving optimized reaction condition, our next move was to explore the scope of the reaction. Initially, the reaction was examined with different substituents on phenyl ring of 2-arylimidazo[1,2-a]pyridines. For this purpose, bromo diethylmalonate **2a** was treated with different 2-arylimidazo[1,2-a]pyridines **1a-1j**. All the para substituted 2-arylimidazo[1,2-a]pyridines with electron donating substituents (such as Me, OMe and halogens) and electron withdrawing substituents on phenyl ring of acetophenone part (**1b-1g**) tolerated the reaction condition with excellent yield (74-92%) (**Scheme 1**). Similarly, 2-(2-naphthyl)imidazo[1,2-a]pyridine **1h** also underwent the reaction to provide the product **3h** in an excellent yield (92%). To check the effect of '*meta'* substitution on our reaction, 2-(3-bromophenyl)imidazo[1,2-a]pyridine **1i** was treated with **2a** under the optimized reaction conditions. Without any surprises it also reacted smoothly to produce the product **3i** in very good yield (77%). To prove the synthetic utility of our protocol in terms of application when bromodiethylmalonate **2a** was reacted with 6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridine **1j**, a very good yield of the product **3j** was obtained (82%). When bromo dimethylmalonate **2b** was used instead of bromo diethylmalonate **2a**, it also sustained the reaction condition and yielded the products **3k** (74%) and **3l** (77%) with very good yields. The protocol was also attempted with isoquinoline **1k** and benzothiazole **1l** but no reaction was observed in both the cases and starting materials were recovered.

In the process of further exploration of this protocol, it was decided to study the scope of the reaction with other class of imidazoheterocycles. For this purpose different 6-aryllimidazo-[2,1-b]-thiazole were synthesized following the reported procedure.[23] When 6-phenylimidazo-[2,1-b]-thiazole **1m** was treated with bromodiethyl malonate **2a** under optimized conditions, the product **3o** was obtained in very good yield (90%) (**Scheme 2**). Similarly, 6-(4-methoxyphenyl)imidazo-[2,1-b]-thiazole **1n** and 6-naphthylimidazo-[2,1-b]-thiazole **1o** also reacted well with bromodiethyl malonate **2a** to produce desired products **3p** (88%) and **3q** (89%) in excellent yields. Presence of electron withdrawing group on phenyl ring also tolerated well under these conditions as 4-(imidazo[2,1-

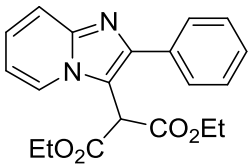
b]thiazol-6-yl)benzonitrile **1p** also gave product **3r** (83%) in a good yield. Bromodimethyl malonate **2b** also reacted smoothly with 6-phenylimidazo-[2,1-b]-thiazole **1m** under our conditions. Next, we chose benzo[d]-imidazo[2,1-b]thiazole as the heterocycle counterpart and bromodiethyl malonate **2a** was treated with 7-methoxy-2-phenylbenzo[d]imidazo[2,1-b]thiazole **1q** to produce the corresponding alkylated product **3t**.

We have also proved the synthetic utility of this protocol by carrying out the total synthesis of drug molecule zolpidem (**Scheme 3**). For this purpose, the product **3j** was subjected to Krapcho decarboxylation to produce **4j** which on hydrolysis and then condensation with amine can yield zolpidem molecule. This protocol can also be applied for the synthesis of Alpidem molecule.[24]

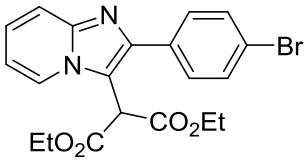


1a-1j

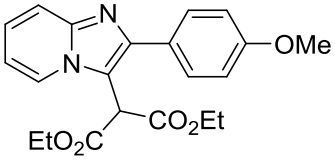
3a-l



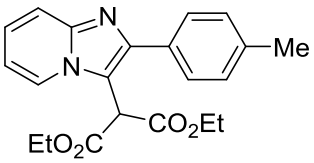
3a (95%)



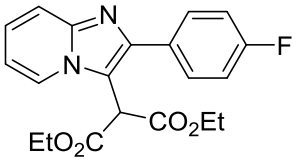
3b (91%)



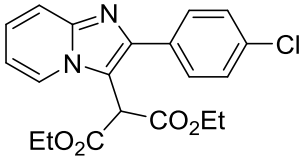
3c (92%)



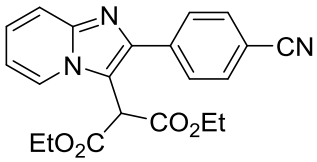
3d (86%)



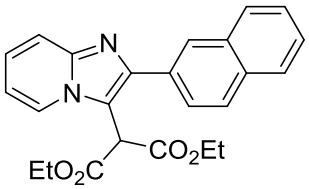
3e (80%)



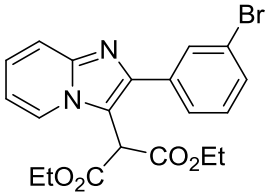
3f (81%)



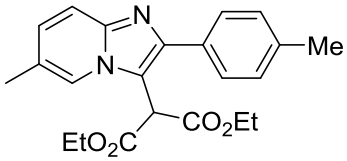
3g (74%)



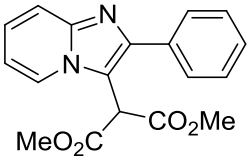
3h (92%)



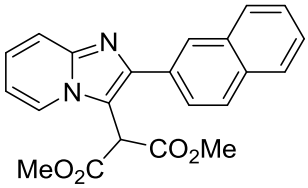
3i (77%)



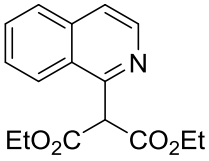
3j



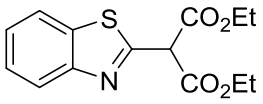
3k (74%)



3l (77%)

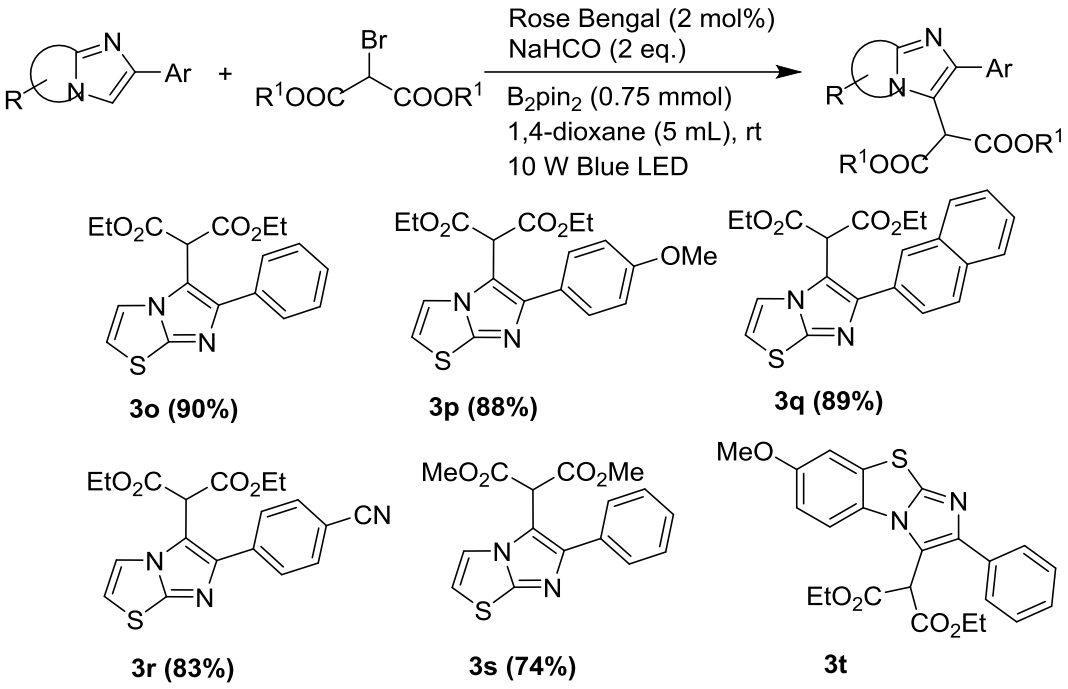


3m (0%)

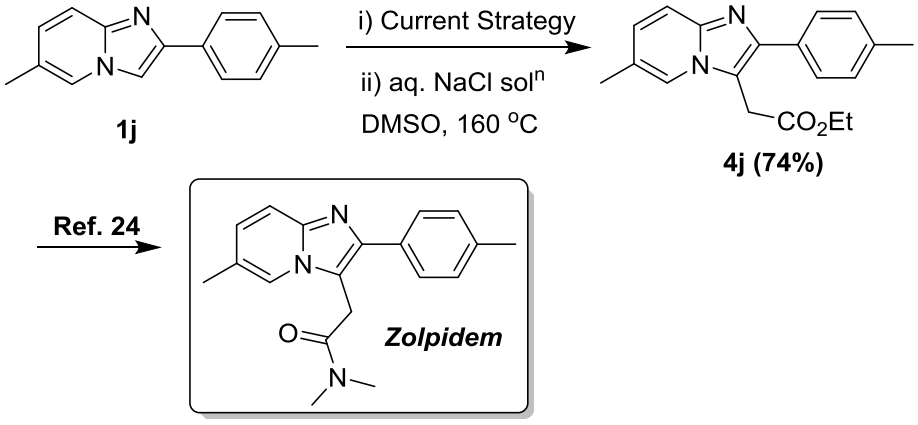


3n (0%)

Scheme 1



Scheme 2

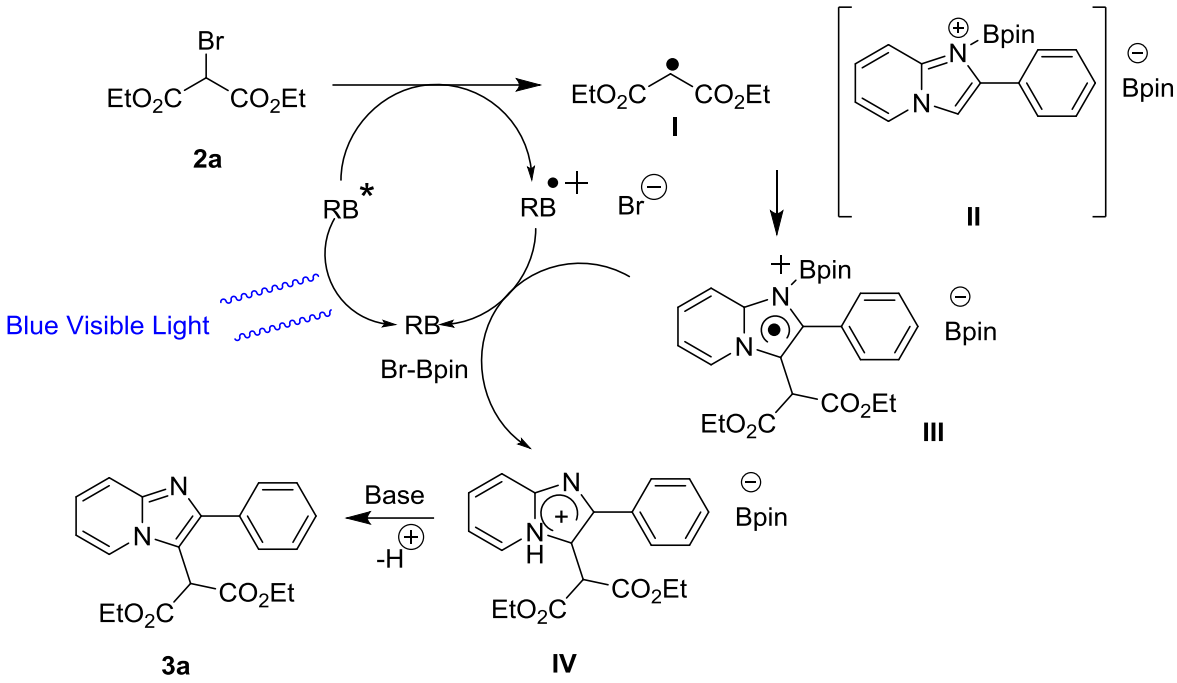


Scheme 3

Few control experiments were carried out to examine the mechanism of the reaction. When 2-phenylimidazo[1,2-a]pyridine **1a** and bromodiethyl malonate **2a** were treated in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) under the optimized reaction conditions, the desired product **3a** was not obtained. Similar result was observed when the same reaction was carried out in the presence of 2,6-di-tert-butyl-4-methyl phenol (BHT). These results indicated that the reaction probably proceeds through a radical pathway. From the optimization studies it was very much clear that 2-phenylimidazo[1,2-a]pyridine **1a** decomposes in the absence of B_2Pin_2 and is necessary to get the desired product. From the above results and previous literature,[16,25] a plausible reaction mechanism was proposed for our reaction protocol (**Scheme**

4). In the presence of blue LED, rose bengal (RB) is converted to its excited state **RB*** which helps in generation of carbon radical species **I** from **2a**. 2-Phenylimidazo[1,2-a]pyridine **1a** gets activated by B_2pin_2 to intermediate **II**. The carbon radical **I** react with intermediate **II** to produce radical intermediate **III** which gets converted to intermediate **IV**. This intermediate **IV** undergoes abstraction of proton by base to produce the final product **3a**.

In conclusion, we have developed a green and sustainable reaction protocol for C_3-alkylation of imidazo[1,2-a]pyridines, imidazo[2,1-b]thiazole and benzo[d]imidazo-[2,1-b]thiazole with active methylene compounds at room temperature. To the best of our knowledge, this is first report for synthesis of these molecules. These molecules can be easily functionalized further to obtain other new functionalized molecules. The substrate scope of above protocol is sufficiently good and the yields of the products are excellent. This protocol has been applied for the synthesis of Zolpidem.



Scheme 4

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Conflicts of Interest:
There are no conflicts to declare.

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